GLOBAL TUBERCULOSIS REPORT

2016

World Health Organization
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## Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>aDSM</td>
<td>active TB drug-safety monitoring and management</td>
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<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
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<td>ART</td>
<td>antiretroviral therapy</td>
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<td>ATP</td>
<td>adenosine triphosphate</td>
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<tr>
<td>BCG</td>
<td>Bacille-Calmette-Guérin</td>
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<tr>
<td>BRICS</td>
<td>Brazil, the Russian Federation, India, China, South Africa</td>
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<tr>
<td>CC</td>
<td>critical concentration</td>
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<tr>
<td>CFR</td>
<td>case fatality ratio</td>
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<td>CHOICE</td>
<td>CHOosing Interventions that are Cost-Effective (WHO)</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CRS</td>
<td>creditor reporting system</td>
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<tr>
<td>DST</td>
<td>drug susceptibility testing</td>
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<tr>
<td>EQA</td>
<td>external quality assessment</td>
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<tr>
<td>FIND</td>
<td>Foundation for Innovative New Diagnostics</td>
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<td>GAF</td>
<td>Global Action Framework for TB Research</td>
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<tr>
<td>GDP</td>
<td>gross domestic product</td>
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<td>GHE</td>
<td>government health expenditures</td>
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<td>GIS</td>
<td>geographic information system</td>
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<td>Global Fund</td>
<td>The Global Fund to Fight AIDS, TB and Malaria</td>
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<td>GTB</td>
<td>Global TB Programme</td>
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<td>HBC</td>
<td>high burden country</td>
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<tr>
<td>HIV</td>
<td>human immune-deficiency virus</td>
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<td>IGRA</td>
<td>interferon gamma release assays</td>
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<tr>
<td>IHME</td>
<td>Institute of Health Metrics and Evaluation</td>
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<tr>
<td>LAMP</td>
<td>loop-mediated isothermal amplification</td>
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<td>LPA</td>
<td>line probe assay</td>
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<td>LTBI</td>
<td>latent TB infection</td>
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<td>MDG</td>
<td>Millennium Development Goal</td>
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<tr>
<td>MDR</td>
<td>multidrug-resistant</td>
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<tr>
<td>MDR/RR-TB</td>
<td>RR-TB cases including MDR-TB cases</td>
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<td>M:F</td>
<td>male to female (ratio)</td>
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<tr>
<td>MSF</td>
<td>Médecins Sans Frontières</td>
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<td>NGO</td>
<td>nongovernmental organization</td>
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<td>NHI</td>
<td>national health insurance</td>
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<td>NTP</td>
<td>national TB programme</td>
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<tr>
<td>OBR</td>
<td>optimized background regimen</td>
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<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<td>OOP</td>
<td>out-of-pocket</td>
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<tr>
<td>PAF</td>
<td>population attributable fraction</td>
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<td>PMDT</td>
<td>programmatic management of drug-resistant TB</td>
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<td>POC</td>
<td>point-of-care</td>
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<tr>
<td>P:N</td>
<td>prevalence to notification (ratio)</td>
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<tr>
<td>PPM</td>
<td>public-private mix</td>
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<tr>
<td>RR</td>
<td>rifampicin-resistant</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
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<tr>
<td>SDG</td>
<td>Sustainable Development Goal</td>
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<td>SHA</td>
<td>System of health accounts</td>
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<td>SNP</td>
<td>single nucleotide polymorphism</td>
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<tr>
<td>SRL</td>
<td>Supranational Reference Laboratory</td>
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<td>SSI</td>
<td>Statens Serum Institute</td>
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<td>STD</td>
<td>sexually transmitted disease</td>
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<td>TB</td>
<td>tuberculosis</td>
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<td>TBTC</td>
<td>TB Trial Consortium</td>
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<td>TBVI</td>
<td>Tuberculosis Vaccine Initiative</td>
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<tr>
<td>TDR</td>
<td>Special Programme for Research and Training in Tropical Diseases</td>
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<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
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<td>TST</td>
<td>tuberculin skin test</td>
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<tr>
<td>UCS</td>
<td>Universal Coverage Scheme (Viet Nam)</td>
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<tr>
<td>UHC</td>
<td>universal health coverage</td>
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<td>UN</td>
<td>United Nations</td>
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<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<td>US</td>
<td>United States</td>
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<tr>
<td>USAID</td>
<td>US Agency for International Development</td>
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<tr>
<td>VR</td>
<td>vital registration</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WRD</td>
<td>WHO-recommended rapid diagnostic</td>
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<tr>
<td>XDR-TB</td>
<td>extensively drug-resistant TB</td>
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</table>
This global TB report was produced by a core team of 18 people: Laura Anderson, Hannah Monica Dias, Dennis Falzon, Katherine Floyd, Inés García Baena, Christopher Gilpin, Philippe Glaziou, Yohhei Hamada, Avinash Kanchar, Irwin Law, Christian Lienhardt, Andrew Siroka, Charalambos Sismanidis, Lana Syed, Hazim Timimi, Wayne van Gemert, Diana Weil and Matteo Zignol. The team was led by Katherine Floyd. Overall guidance was provided by the Director of the WHO Global TB Programme, Mario Raviglione.

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WHO Region of the Americas


WHO Eastern Mediterranean Region


WHO European Region

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WHO South-East Asia Region


WHO Western Pacific Region

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WHO South-East Asia Region

WHO Western Pacific Region
Global actions and investments fall far short of those needed to end the global TB epidemic.
Executive Summary

Background

The Sustainable Development Goals (SDGs) for 2030 were adopted by the United Nations in 2015. One of the targets is to end the global TB epidemic. The WHO End TB Strategy, approved by the World Health Assembly in 2014, calls for a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate by 2030, compared with 2015.

This global TB report is the first to be produced in the era of the SDGs and the End TB Strategy. It provides an assessment of the TB epidemic and progress in TB diagnosis, treatment and prevention efforts, as well as an overview of TB-specific financing and research. It also discusses the broader agenda of universal health coverage, social protection and other SDGs that have an impact on health. Data were available for 202 countries and territories that account for over 99% of the world’s population and TB cases.

Main findings and messages

Status of the TB epidemic and MDR-TB crisis

The TB epidemic is larger than previously estimated, reflecting new surveillance and survey data from India. However, the number of TB deaths and the TB incidence rate continue to fall globally and in India.

In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases.

Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa. Global progress depends on major advances in TB prevention and care in these countries. Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015. This needs to accelerate to a 4–5% annual decline by 2020 to reach the first milestones of the End TB Strategy.

In 2015, there were an estimated 580,000 new cases eligible for MDR-TB treatment, only 125,000 (20%) were enrolled. Five countries accounted for more than 60% of the gap: India, China, the Russian Federation, Indonesia and Nigeria. Globally, the MDR-TB treatment success rate was 52% in 2013.

In 2015, 55% of notified TB patients had a documented HIV test result. The proportion of HIV-positive TB patients on antiretroviral therapy (ART) was 78%.

Access to TB preventive treatment needs to be expanded. A total of 910,000 people living with HIV were started on such treatment in 2015, as well as 87,000 children under five (7% of those eligible).

TB financing, universal health coverage, social protection and social determinants

US$ 6.6 billion was available for TB care and prevention in low and middle-income countries in 2016, of which 84% was from domestic sources. Nonetheless, national TB programmes (NTPs) in low-income countries continue to rely on international donors for almost 90% of their financing. Investments in low and middle-income countries fall almost US$ 2 billion short of the US$ 8.3 billion needed in 2016. This annual gap will widen to US$ 6 billion in 2020 if current funding levels do not increase.

Improvements are also needed in overall health financing. Government expenditures on health in 2014 were less than the WHO benchmark of at least 6% of gross domestic product (GDP) in 150 countries. Out-of-pocket expenditures exceeded 45% of total health expenditures in 46 countries, including 11 of the 30 high TB burden countries.

TB research and development

Despite some progress in the pipeline for new diagnostics, drugs and regimens, and vaccines, TB research and development remains severely underfunded.
Additional highlights from the report

A new era of global TB monitoring

The End TB Strategy has three high-level indicators: the TB incidence rate, the absolute number of TB deaths and the percentage of TB patients and their households that experience catastrophic costs as a result of TB disease. Targets for these indicators have been set for 2030 and 2035, with accompanying milestones for 2020 and 2025.

The 2020 milestones of the End TB Strategy are a 35% reduction in the absolute number of TB deaths and a 20% reduction in the TB incidence rate, compared with levels in 2015; and that no TB-affected households face catastrophic costs.

WHO has defined three lists of high burden countries for the period 2016–2020, for TB, TB/HIV and MDR-TB. Each list includes 30 countries.

TB disease burden

Upward revisions to estimates of the burden of TB disease in India for the period 2000–2015 follow accumulating evidence that previous estimates were too low. This evidence includes household surveys, a state-wide TB prevalence survey, studies of anti-TB drug sales in the private sector, notification data and new analysis of mortality data. Since India accounts for more than one quarter of the world’s TB cases and deaths, these revisions have had a major impact on global estimates. Estimates for India are considered interim, pending a national TB prevalence survey scheduled for 2017/2018.

The proportion of TB cases living with HIV was highest in the WHO African Region (31%), and exceeded 50% in five countries. WHO has defined three lists of high burden countries for the period 2016–2020, for TB, TB/HIV and MDR-TB.

The only WHO-recommended rapid diagnostic test for detection of TB and rifampicin resistance currently available is the Xpert MTB/RIF® assay. Of the 48 countries in at least one of the three new lists of high burden countries, 15 had adopted national algorithms positioning Xpert MTB/ RIF as the initial diagnostic test for all people with signs and symptoms of pulmonary TB by the end of 2015. These countries accounted for 10% of the estimated global number of incident TB cases in 2015.

In 2015, 30% of the 3.4 million new bacteriologically confirmed and previously treated TB cases notified globally were reported to have had drug susceptibility testing for rifampicin, with coverage of 24% for new TB patients and 53% for previously treated TB patients.

Diagnosis and treatment: TB, HIV-associated TB and drug-resistant TB

The global male:female (M:F) ratio for notifications was 1.7, varying from 1.0 in Pakistan to 3.1 in Viet Nam among the 30 high TB burden countries. Results from national TB prevalence surveys of adults show higher M:F ratios, indicating that notification data underestimate the share of the TB burden accounted for by men in some countries. Globally, children (aged <15 years) accounted for 6.3% of the new cases that were notified in 2015.

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In 2015, the gap of 4.3 million between notifications of new cases and the estimated number of incident cases reflects a mixture of underreporting of detected TB cases (especially in countries with large private sectors) and underdiagnosis (especially in countries where there are major geographic or financial barriers to accessing care).

Ten countries accounted for 77% of the total estimated gap: India, Indonesia, Nigeria, Pakistan, South Africa, Bangladesh, the Democratic Republic of the Congo, China, the United Republic of Tanzania and Mozambique.

In the African Region where the burden of HIV-associated TB is highest, 81% of notified TB patients had a documented HIV test result. The proportion of known HIV-positive TB patients on ART was above 90% in India, Kenya, Malawi, Mozambique, Namibia and Swaziland.

The latest treatment outcome data show a treatment success rate of 83% for TB (2014 cohort), 52% for MDR-TB (2013 cohort) and 28% for extensively drug-resistant TB (XDR-TB; 2013 cohort).

At least 23 countries in Africa and Asia have introduced shorter regimens for treatment of MDR-TB or RR-TB. These have achieved high treatment success rates (87–90%) under operational research conditions. A standardised regimen of 9–12 months is recommended by WHO for all patients (excluding pregnant women) with pulmonary MDR/RR-TB that is not resistant to second-line drugs.

As part of efforts to improve outcomes for MDR/XDR- TB, at least 70 countries had started using bedaquiline and 39 countries had introduced delamanid by the end of 2015.
TB prevention services

South Africa accounted for the largest share (45%) of people living with HIV who received TB preventive treatment for latent TB infection (LTBI) in 2015, followed by Malawi, Mozambique and Kenya. Ten countries reported data for the first time, including Kenya. Despite this progress, 21 of the 30 high TB/HIV burden countries did not report data.

The ratio of the TB notification rate among health-care workers to the TB notification rate in the general adult population is a good indicator of the impact of TB infection control in health facilities. In 16 countries, the number of TB cases per 100,000 health-care workers was more than double the notification rate in the general adult population in 2015.

BCG vaccination should be provided as part of national childhood immunization programmes according to a country's TB epidemiology. In 2015, 163 countries reported providing BCG vaccination as a standard part of these programmes; 102 reported coverage of above 90%.

Universal health coverage, social protection and addressing social determinants: Implications for TB

In some high TB burden settings, emerging health financing schemes, including national health insurance, could lead to major reductions in out-of-pocket expenditures in low-income populations. Thailand and a range of countries in the Region of the Americas are good pathfinding examples.

Building on established approaches to private engagement in TB care could help to address the burgeoning private sector in health-care delivery, especially in Asia. This includes a combination of provider incentives and regulation, and application of innovative institutional intermediaries and communications technologies. Such levers can help to assure the quality of services provided.

Social protection can be advanced through better models of care and social benefits. Many low- and middle-income countries have financed social and economic support for TB patients, but these support packages need to be better documented and evaluated. For overall impact and sustainability, using national social protection platforms is a priority.

WHO-recommended baseline national surveys are underway to assess the nature and severity of TB patient costs, and to improve service delivery and social protection accordingly. One country survey was conducted in 2015, eight began in 2016 and ten are planned for 2017–2018.

The available evidence about links between ending TB and ending poverty needs to be used to advocate for poverty elimination and action on related risk factors, such as noncommunicable disease prevention, food security, and housing.

TB financing

The BRICS countries (Brazil, the Russian Federation, India, China and South Africa), which collectively account for about 50% of the world’s TB cases, rely mostly or exclusively (the exception is India) on domestic funding.

In other countries with a high TB burden, international donor funding dominates, accounting for 75% of reported funding for NTPs in the group of 25 high TB burden countries outside BRICS, 87% of funding in low-income countries and 60% of funding in lower middle-income countries. The single largest source of international donor funding is the Global Fund to Fight AIDS, Tuberculosis and Malaria.

International donor funding for TB falls far short of donor contributions for HIV and malaria. The latest data from the Organisation for Economic Co-operation and Development (OECD) creditor reporting system show totals of US$ 5.4 billion for HIV/AIDS, US$ 1.7 billion for malaria and US$ 0.7 billion for TB in 2014.

The cost per patient treated is usually in the range of US$ 100-1000 for drug-susceptible TB and US$ 2000-20,000 for MDR-TB.

TB research and development

At least US$ 2 billion per year is needed for TB research and development. Funding during the decade 2005–2014 never exceeded US$ 0.7 billion per year.

In 2016, four diagnostic tests were reviewed and recommended by WHO: the loop-mediated isothermal amplification test for TB (known as TB-LAMP), two line probe assays (LPAs) for the detection of resistance to the first-line anti-TB drugs isoniazid and rifampicin, and an LPA for the detection of resistance to second-line anti-TB drugs. A next-generation cartridge called Xpert Ultra and a new diagnostic platform called GeneXpert Omni are in development; assessment of both by WHO is expected in 2017.

There are nine drugs in advanced phases of clinical trials for the treatment of drug-susceptible TB, drug-resistant TB or LTBI. These are bedaquiline, delamanid, linezolid, PBTZ169, pretomanid, Q203, rifampicin (high-dose), rifapentine and sutezolid.

There are 13 vaccine candidates in clinical trials, including candidates for prevention of TB infection and candidates for prevention of TB disease in people with LTBI.

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1 Countries are listed in descending order of their number of cases.
2 MDR-TB is defined as resistance to rifampicin and isoniazid. WHO recommends that all patients with rifampicin-resistant TB (RR-TB) are treated with a second-line MDR-TB regimen. Cases of MDR-TB and RR-TB are collectively referred to as MDR/RR-TB in this report.
3 When an HIV-positive person dies from TB disease, the underlying cause is classified as HIV in the International Classification of Diseases system (ICD-10).
4 i.e. 10.4 million minus 6.1 million.
5 Countries are listed in descending order of the size of their gap.
6 This is the latest year for which treatment outcome data are currently available.
Box 1.1
Basic facts about TB

TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It typically affects the lungs (pulmonary TB) but can also affect other sites (extrapulmonary TB). The disease is spread when people who are sick with pulmonary TB expel bacteria into the air, for example by coughing. Overall, a relatively small proportion (5-15%) of the estimated 2-3 billion people infected with M. tuberculosis will develop TB disease during their lifetime. However, the probability of developing TB disease is much higher among people infected with HIV.

Diagnostic tests for TB disease include:

- sputum smear microscopy. This was developed more than 100 years ago. Sputum samples are examined under a microscope to see if bacteria are present. In the current case definitions recommended by WHO, one positive result is required for a diagnosis of smear-positive pulmonary TB;
- rapid molecular tests. The only rapid test for diagnosis of TB currently recommended by WHO is the Xpert® MTB/RIF assay (Cepheid, Sunnyvale USA). It was initially recommended (in 2010) for diagnosis of pulmonary TB in adults. Since 2013, it has also been recommended for children and specific forms of extrapulmonary TB. The test has much better accuracy than microscopy; and
- culture methods. These are the current reference standard but require more developed laboratory capacity and can take up to 12 weeks to provide results.

Globally, use of rapid molecular tests is increasing, and many countries are phasing out use of smear microscopy for diagnostic purposes (although microscopy and culture remain necessary for treatment monitoring). Despite advances in diagnostics, a considerable proportion of the TB cases reported to WHO are still clinically diagnosed rather than bacteriologically confirmed. In 2015, for example, 57% of the pulmonary cases reported to WHO were bacteriologically confirmed.

There are also tests for TB that is resistant to first and second-line anti-TB drugs. They include Xpert MTB/RIF, which simultaneously tests for TB and resistance to rifampicin (the most effective first-line anti-TB drug); rapid line probe assays (LPAs) that test for resistance to rifampicin and isoniazid (referred to as first-line LPAs); a rapid LPA that tests for resistance to fluoroquinolones and injectable anti-TB drugs (referred to as a second-line LPA); and sequencing technologies. First-line LPAs were first recommended by WHO in 2008; the second-line LPA was first recommended in May 2016. Culture-based methods currently remain the reference standard for drug susceptibility testing.

Without treatment, the death rate from TB is high. Studies of the natural history of TB disease in the absence of treatment with anti-TB drugs (that were conducted before drug treatments became available) found that about 70% of people with sputum smear-positive pulmonary TB died within 10 years, as did about 20% of people with culture-positive (but smear-negative) pulmonary TB.

Effective drug treatments were first developed in the 1940s. The currently recommended treatment for new cases of drug-susceptible TB is a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. The Global TB Drug Facility supplies a complete 6-month course for about US$ 40 per person. Treatment success rates of at least 85% for new cases of drug-susceptible TB are regularly reported to WHO by its 194 Member States. Treatment for rifampicin-resistant TB (RR-TB) and multidrug-resistant TB (MDR-TB) is longer, and requires more expensive and more toxic drugs. Until early 2016, the treatment regimens recommended by WHO typically lasted for 20 months, and cost about US$ 2000–5000 per person. As a result of new evidence from several countries, WHO issued updated guidance in May 2016. A standardised shorter MDR-TB regimen of 9-12 months is now recommended for all patients (excluding pregnant women) with pulmonary MDR/RR-TB that is not resistant to second-line drugs. The cost of a shortened drug regimen is about US$ 1000 per person.

New TB drugs have begun to emerge from the pipeline, and combination regimens that include new compounds are being tested in clinical trials. The Bacille-Calmette-Guérin (BCG) vaccine, which was developed almost 100 years ago and has been shown to prevent severe forms of TB in children, is widely used. However, there is currently no vaccine that is effective in preventing TB disease in adults, either before or after exposure to TB infection. There are 13 TB vaccines in Phase I, Phase II or Phase III trials.

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b. Defined as resistance to isoniazid and rifampicin, the two most powerful anti-TB drugs.
Chapter 1: Introduction

Tuberculosis (TB) has existed for millennia and remains a major global health problem. It causes ill-health in millions of people each year and in 2015 was one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease.\(^1\) This is despite the fact that with a timely diagnosis and correct treatment, most people who develop TB disease can be cured. Basic facts about TB are summarized in Box 1.1.

The best estimate is that there were 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among HIV-positive people.\(^2\) In terms of cases, the best estimates for 2015 are that there were 10.4 million new TB cases (including 1.2 million among HIV-positive people), of which 5.9 million were among men, 3.5 million among women and 1.0 million among children. Overall, 90% of cases were adults and 10% children, and the male:female ratio was 1.6:1.

WHO has published a global TB report every year since 1997. The main aim of the report is to provide a comprehensive and up-to-date assessment of the TB epidemic, and of progress in prevention, diagnosis and treatment of the disease at global, regional and country levels. This is done in the context of recommended global TB strategies and targets endorsed by WHO’s Member States and broader development goals set by the United Nations (UN).

As usual, the 2016 global TB report is based primarily on data gathered from countries and territories. WHO has implemented annual rounds of global TB data collection since 1996, with an online system\(^3\) used since 2009. In 2016, this system was opened for reporting at the end of March. Following the May deadline for reporting and subsequent review and follow-up of submitted data between June and August, data were available for 202 countries and territories that account for more than 99% of the world’s population and estimated TB cases; this included 183 of WHO’s 194 Member States.

Other sources of data used in 2016 include the HIV department in WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS), which collect information about the provision of TB preventive treatment to people living with HIV and about antiretroviral therapy for HIV-positive TB patients; the creditor reporting system of the Organisation for Economic Co-operation and Development (OECD); the World Bank, for development indicators; and the WHO national health accounts database.

This is the first global TB report to be produced in the post-2015 era of the Sustainable Development Goals (SDGs) and the End TB Strategy, which have superseded the Millennium Development Goals (2000–2015) and the Stop TB Strategy (2006–2015), respectively. The SDGs were adopted by the UN in September 2015 and cover the period 2016–2030. The End TB Strategy spans a 20-year timeframe (2016–2035) and was unanimously endorsed by WHO’s Member States at the 2014 World Health Assembly. The SDGs and the End TB Strategy share a common aim: to end the global TB epidemic. Targets set in the End TB Strategy include a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030, compared with 2015.

In this new context, the structure and content of the global TB report have been reshaped. Chapter 2 provides an overview of the SDGs, the End TB Strategy and new lists of high burden countries (for TB, TB/HIV and drug-resistant TB) that will be given particular attention in the period 2016–2020. The remaining six chapters of the report cover TB disease burden; diagnosis and treatment of TB, HIV-associated TB and drug-resistant TB; TB prevention services; universal health coverage, social protection and social determinants from the TB perspective; TB financing; and TB research and development.

The report also has four annexes. Annex 1 explains how to access the online WHO global TB database and provides further details about the 2016 round of global TB data collection. Annex 2 contains country profiles for the 30 high TB burden countries (profiles for other countries are available online\(^4\)) and Annex 3 contains profiles for WHO’s six regions. Annex 4 provides data tables that give details of key indicators for the most recent year for which data or estimates are available, for all countries.

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\(^1\) In 2015, there were an estimated 1.1 million deaths due to HIV, including 0.4 million deaths from TB among HIV-positive people (see unaids.org).

\(^2\) When an HIV-positive person dies from TB disease, the underlying cause is classified as HIV in the international classification of diseases system.

\(^3\) https://extranet.who.int/tme

\(^4\) www.who.int/tb/data
Chapter 2 :: A new era of global TB monitoring

From 2000 to 2015, global and national efforts to reduce the burden of tuberculosis (TB) disease were focused on achieving targets set within the context of the Millennium Development Goals (MDGs). The MDGs were established by the United Nations (UN) in 2000 and targets were set for 2015. Target 6c of MDG6 was to “halt and reverse” TB incidence. The Stop TB Partnership, established in 2001, adopted this target and set two additional targets: that TB prevalence and TB mortality rates should be halved by 2015 compared with their levels in 1990. The global TB strategy developed by WHO for the decade 2006–2015, the Stop TB Strategy, had the overall goal of reaching all three targets.

WHO published its assessment of whether the 2015 global TB targets for reductions in TB incidence, prevalence and mortality were achieved in October 2015. The assessment indicated that the MDG target was achieved on a worldwide basis, in each of WHO’s six regions and in 16 of the 22 countries that were classified by WHO as high TB burden countries during the period 2002–2015. Globally, the TB mortality rate fell by 47% between 1990 and 2015, with most of that improvement occurring after 2000. The target of a 50% reduction was met in four WHO regions – the Region of the Americas, the Eastern Mediterranean Region, the South-East Asia Region and the Western Pacific Region – and in 11 high TB burden countries. Globally, TB prevalence fell by 42% between 1990 and 2015. The target of a 50% reduction was achieved in three WHO regions – the Region of the Americas, the South-East Asia Region and the Western Pacific Region – and in nine high TB burden countries.

The MDGs (2000–2015) have now been superseded by the Sustainable Development Goals (SDGs), which have an end date of 2030. Similarly, WHO’s Stop TB Strategy has been replaced by the End TB Strategy, which covers the period 2016–2035. With the Global tuberculosis report 2016 being the first such report in the post-2015 era, this chapter provides an overview of both the SDGs (Section 2.1) and the End TB Strategy (Section 2.2), including the indicators that will be used to monitor progress. For the first 5 years of this new era (2016–2020), WHO has also defined updated lists of high burden countries (HBCs) for TB, TB/HIV and multidrug-resistant TB (MDR-TB). The updated lists are presented and explained in Section 2.3.

2.1 The Sustainable Development Goals

The SDGs were adopted by all UN Member States in September 2015, at the UN General Assembly. The 17 goals are shown in Box 2.1. Departures from the MDGs include a broader agenda (17 goals compared with the previous eight), one consolidated goal on health compared with three health-related MDGs, and a desire for universal relevance rather than a focus on issues mostly of concern to developing countries.

SDG3 is to “Ensure healthy lives and promote well-being for all at all ages”, and it includes 13 targets (Box 2.2). One of these targets, Target 3.3, explicitly mentions TB: “By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases, and combat hepatitis, water-borne diseases and other communicable diseases”. The language of “ending epidemics” is also now a prominent element of global health strategies developed by WHO and the Joint United Nations Programme on HIV/AIDS (UN-AIDS) for the post-2015 era, including the End TB Strategy (Section 2.2). Such language is much more ambitious than the MDG language of “halting and reversing” epidemics (or “stopping” them, as in the Stop TB Strategy). The TB indicator for Target 3.3 is TB incidence per 100 000 population.

SDG3 also includes a target (Target 3.8) related to universal health coverage (UHC). The WHO/World Bank definition of UHC is that all people receive the health services they need, while at the same time ensuring that the use of these services does not expose the user to financial hardship.

Indicators for Target 3.8 include coverage of tracer interventions for prevention and treatment (including TB treatment coverage), and financial coverage provided by health insurance or a public health system.

Across the SDG indicator framework as a whole, the definitions of many indicators include much greater emphasis on within-country disaggregation compared with the MDGs. This includes disaggregation by age, sex, geog-
:: Box 2.1

The Sustainable Development Goals

Goal 1. End poverty in all its forms everywhere
Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture
Goal 3. Ensure healthy lives and promote well-being for all at all ages
Goal 4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all
Goal 5. Achieve gender equality and empower all women and girls
Goal 6. Ensure availability and sustainable management of water and sanitation for all
Goal 7. Ensure access to affordable, reliable, sustainable and modern energy for all
Goal 8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all
Goal 9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation
Goal 10. Reduce inequality within and among countries
Goal 11. Make cities and human settlements inclusive, safe, resilient and sustainable
Goal 12. Ensure sustainable consumption and production patterns
Goal 13. Take urgent action to combat climate change and its impacts
Goal 14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development
Goal 15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss
Goal 16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels
Goal 17. Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development

Acknowledging that the United Nations Framework Convention on Climate Change is the primary international, intergovernmental forum for negotiating the global response to climate change
SDG3: Ensure healthy lives and promote well-being for all at all ages

**Targets**

3.1 By 2030, reduce the global maternal mortality ratio to less than 70 per 100 000 live births

3.2 By 2030, end preventable deaths of new-borns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases

3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and wellbeing

3.5 Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol

3.6 By 2020, halve the number of global deaths and injuries from road traffic accidents

3.7 By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all

3.9 By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination

3.a Strengthen the implementation of the World Health Organization Framework Convention on Tobacco Control in all countries, as appropriate

3.b Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade-Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all

3.c Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States

3.d Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks

**Box 2.2**

Sustainable Development Goal 3 and its 13 targets

**SDG3:** Ensure healthy lives and promote well-being for all at all ages

**Targets**

3.1 By 2030, reduce the global maternal mortality ratio to less than 70 per 100 000 live births

3.2 By 2030, end preventable deaths of new-borns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

3.3 By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases

3.4 By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and wellbeing

3.5 Strengthen the prevention and treatment of substance abuse, including narcotic drug abuse and harmful use of alcohol

3.6 By 2020, halve the number of global deaths and injuries from road traffic accidents

3.7 By 2030, ensure universal access to sexual and reproductive health-care services, including for family planning, information and education, and the integration of reproductive health into national strategies and programmes

3.8 Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all

3.9 By 2030, substantially reduce the number of deaths and illnesses from hazardous chemicals and air, water and soil pollution and contamination

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3.c Substantially increase health financing and the recruitment, development, training and retention of the health workforce in developing countries, especially in least developed countries and small island developing States

3.d Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks

**2.2 The End TB Strategy**

In 2012, in anticipation of the end of the eras of the MDGs and Stop TB Strategy, WHO’s Global TB Programme initiated the development of a post-2015 global TB strategy. Following 2 years of consultations, the proposed strategy was discussed at the 2014 World Health Assembly, where it was unanimously endorsed by all Member States. That strategy is now known as the End TB Strategy.

The End TB Strategy “at a glance” is shown in Box 2.3. It covers the period 2016–2035 and the overall goal is to “End the global TB epidemic”, defined as around 10 new cases per 100 000 population per year. This is the level found in countries considered to have a low burden of TB in 2015 (Chapter 3).

The End TB Strategy has three high-level, overarching indicators and related targets (for 2030, linked to the SDGs, and for 2035) and milestones (for 2020 and 2025). The three indicators are:


Box 2.3
The End TB Strategy at a glance

**VISION**

A WORLD FREE OF TB
— zero deaths, disease and suffering due to TB

**GOAL**

END THE GLOBAL TB EPIDEMIC

<table>
<thead>
<tr>
<th>INDICATORS</th>
<th>MILESTONES</th>
<th>TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)</td>
<td>35%</td>
<td>75%</td>
</tr>
<tr>
<td>Percentage reduction in the TB incidence rate (compared with 2015 baseline)</td>
<td>20%</td>
<td>50%</td>
</tr>
<tr>
<td>Percentage of TB-affected households experiencing catastrophic costs due to TB (level in 2015 unknown)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**INDICATORS**

**MILESTONES**

<table>
<thead>
<tr>
<th>2020</th>
<th>2025</th>
<th>SDG 2030*</th>
<th>END TB 2035</th>
</tr>
</thead>
</table>

**PRINCIPLES**

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

**PILLARS AND COMPONENTS**

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION
   A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
   B. Treatment of all people with TB including drug-resistant TB, and patient support
   C. Collaborative TB/HIV activities, and management of comorbidities
   D. Preventive treatment of persons at high risk, and vaccination against TB

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS
   A. Political commitment with adequate resources for TB care and prevention
   B. Engagement of communities, civil society organizations, and public and private care providers
   C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
   D. Social protection, poverty alleviation and actions on other determinants of TB

3. INTENSIFIED RESEARCH AND INNOVATION
   A. Discovery, development and rapid uptake of new tools, interventions and strategies
   B. Research to optimize implementation and impact, and promote innovations

* Targets linked to the Sustainable Development Goals (SDGs).
the number of TB deaths per year;
- the TB incidence rate per year; and
- the percentage of TB-affected households that experience catastrophic costs as a result of TB disease.

The 2035 targets are a 95% reduction in TB deaths and a 90% reduction in the TB incidence rate, compared with levels in 2015. The 2030 targets are a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate, compared with levels in 2015. The most immediate milestones, set for 2020, are a 35% reduction in TB deaths and a 20% reduction in the TB incidence rate, compared with levels in 2015. The Stop TB Partnership has developed a Global Plan to End TB, 2016–2020,1 which focuses on the actions and funding needed to reach these 2020 milestones. More details about this plan are provided in Chapter 7.

For the third indicator (the percentage of TB-affected households that experience catastrophic costs as a result of TB disease), the milestone for 2020 is zero, to be sustained thereafter. This indicator is a good tracer for progress towards UHC. If UHC is in place, then people with TB should be able to access high-quality diagnosis and treatment with financial protection; that is, they should not face catastrophic costs.

UHC is also fundamental to achieving the targets for reductions in TB cases and deaths, for two reasons. First, reaching the milestones for reductions in cases and deaths set for 2020 and 2025 requires the annual decline in the global TB incidence rate to accelerate from 1.5% per year in 2015 to 4–5% per year by 2020, and then to 10% per year by 2025. A decline of 10% per year is equivalent to the best-ever performance at national level historically – for example, in countries in western Europe during the 1950s and 1960s. Declines of 10% per year have only been documented in the context of UHC (and of broader social and economic development). Second, the global proportion of people with TB who die from the disease (i.e. the CFR) needs to be reduced to 10% by 2020 and then to 6.5% by 2025. A CFR of 6.5% is similar to the current level in many high-income countries but is only possible if all those with TB disease can access high-quality treatment. Analysis of CFRs across and within countries is included in Chapter 3.

After 2025, an unprecedented acceleration in the rate at which TB incidence falls globally is required if the 2030 and 2035 targets are to be reached. Such an acceleration will depend on a technological breakthrough – for example, a post-exposure vaccine or a short, efficacious and safe treatment for latent TB infection (LTBI) – so that the risk of developing TB disease among the approximately 2–3 billion people who are already infected with Mycobacterium tuberculosis is substantially reduced. The trajectories of TB incidence and TB deaths that are required to reach End TB Strategy milestones and targets are shown in Fig. 2.1, and the latest status of the development pipelines for new diagnostics, drugs and vaccines is presented in Chapter 8.

This report includes estimates of trends in TB incidence and mortality for the period 2000–2015 (Chapter 3). In contrast to previous global TB reports, estimates of TB prevalence are not shown for all countries. This is because (unlike the era of the MDGs and Stop TB Strategy) TB prev-

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### Table 2.1

Top 10 indicators (not ranked) for monitoring implementation of the End TB Strategy at global and national levels, with recommended target levels that apply to all countries. The target level is for 2025 at the latest.

<table>
<thead>
<tr>
<th>INDICATOR</th>
<th>RECOMMENDED TARGET LEVEL</th>
<th>MAIN RATIONALE FOR INCLUSION IN TOP 10</th>
<th>MAIN METHOD OF MEASUREMENT, AND CHAPTER OF THIS REPORT WHERE INDICATOR IS FEATURED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. TB treatment coverage</td>
<td>≥90%</td>
<td>High-quality TB care is essential to prevent suffering and death from TB and to cut transmission. High coverage of appropriate treatment is a fundamental requirement for achieving the milestones and targets of the End TB Strategy.</td>
<td>Routinely collected notification data used in combination with estimate of TB incidence. Chapter 4</td>
</tr>
<tr>
<td>2. TB treatment success rate</td>
<td>≥90%</td>
<td></td>
<td>Routinely collected data. Chapter 4</td>
</tr>
<tr>
<td>3. Percentage of TB-affected households that experience catastrophic costs due to TB</td>
<td>0%</td>
<td>One of the End TB Strategy’s three high-level indicators; a key marker of financial risk protection (one of the two key elements of UHC) and social protection for TB-affected households.</td>
<td>National survey of notified TB patients. Chapter 6</td>
</tr>
<tr>
<td>4. Percentage of new and relapse TB patients tested using a WHO-recommended rapid diagnostic (WRD) at the time of diagnosis</td>
<td>≥90%</td>
<td>Accurate diagnosis is a fundamental component of TB care. Rapid molecular diagnostic tests help to ensure early detection and prompt treatment.</td>
<td>Routinely collected data (as part of case-based surveillance), or national survey of medical records or patient cards of TB patients. Chapter 4</td>
</tr>
<tr>
<td>5. Latent TB infection (LTBI) treatment coverage</td>
<td>≥90%</td>
<td>Treatment of LTBI is the main treatment intervention available to prevent development of active TB disease in those already infected with Mycobacterium tuberculosis.</td>
<td>Routinely collected data (as part of case-based surveillance), or national survey of medical records or patient cards of people living with HIV and TB patients. Chapter 5</td>
</tr>
<tr>
<td>6. Contact investigation coverage</td>
<td>≥90%</td>
<td>Contact tracing is a key component of TB prevention, especially in children.</td>
<td>As above for LTBI.</td>
</tr>
<tr>
<td>7. Drug-susceptibility testing (DST) coverage for TB patients</td>
<td>100%</td>
<td>Testing for drug susceptibility for WHO-recommended drugs is essential to provide the right treatment for every person diagnosed with TB.</td>
<td>Routinely collected data (as part of case-based surveillance), or national survey of medical records or patient cards of TB patients. Chapter 4</td>
</tr>
<tr>
<td>8. Treatment coverage, new TB drugs</td>
<td>≥90%</td>
<td>An indicator that is relevant to monitoring the adoption of innovations in all countries.</td>
<td>As above for DST.</td>
</tr>
<tr>
<td>9. Documentation of HIV status among TB patients</td>
<td>100%</td>
<td>One of the core global indicators used to monitor collaborative TB/HIV activities. Documentation of HIV status is essential to provide the best care for HIV-positive TB patients, including antiretroviral therapy.</td>
<td>Routinely collected data for all TB patients. Chapter 4</td>
</tr>
<tr>
<td>10. Case fatality ratio (CFR)</td>
<td>≤5%</td>
<td>This is a key indicator for monitoring progress towards the 2020 and 2025 milestones. A CFR of 6% is required to achieve the 2025 global milestone for reductions in TB deaths and cases.</td>
<td>Mortality divided by incidence. In countries with a high-performance surveillance system, notifications approximate incidence. Chapter 3, Chapter 6</td>
</tr>
</tbody>
</table>

CFR, case fatality ratio; DST, drug-susceptibility testing; HIV, human immunodeficiency virus; LTBI, latent TB infection; SDG, Sustainable Development Goal; TB, tuberculosis; UHC, universal health care; WHO, World Health Organization; WRD, WHO-recommended rapid diagnostic.

* Catastrophic costs are provisionally defined as total costs that exceed 20% of annual household income.
alence is no longer a high-level indicator for which a global target has been set. However, national TB prevalence surveys remain important for assessing TB disease burden and trends (through repeat surveys) in many countries, and can also inform estimates of TB incidence. For these reasons, results from recent national TB prevalence surveys are included in Chapter 3.

To achieve the targets and milestones, the End TB Strategy has four underlying principles and three pillars. The principles are: government stewardship and accountability, with monitoring and evaluation; a strong coalition with civil society organizations and communities; protection and promotion of human rights, ethics and equity; and adaptation of the strategy and targets at country level, with global collaboration. The three pillars are: integrated, patient-centred TB care and prevention; bold policies and supportive systems; and intensified research and innovation.

The 10 components of the three pillars are shown in Box 2.3 and the 10 priority indicators (defined in March 2015 in association with the publication of a journal article about the End TB Strategy)\(^1\) to monitor their implementation are shown in Table 2.1. The chapter of this report in which available data for each indicator can be found is also explained in the table.

Data for 5 of the 10 indicators cannot be captured routinely using the standard recording and reporting forms for paper-based systems that are included in the latest revision of WHO’s framework for TB case definitions and reporting.\(^2\) Collection of data on the costs faced by TB patients and their households and assessment of whether these are catastrophic (indicator 3 in Table 2.1) requires periodic surveys of a representative sample of TB patients; further details are provided in Chapter 6. For the other four indicators (numbered 4, 5, 6 and 8 in Table 2.1), data may already be captured routinely in countries with electronic case-based systems for recording and reporting of data, or these systems can be adapted to do so. Alternatively, periodic surveys of the medical records or patient cards of a random sample of TB patients can be done. Further guidance is provided in WHO operational guidance on the

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### Table 2.2

<table>
<thead>
<tr>
<th>LIST</th>
<th>THE 30 HIGH TB BURDEN COUNTRIES</th>
<th>THE 30 HIGH TB/HIV BURDEN COUNTRIES</th>
<th>THE 30 HIGH MDR-TB BURDEN COUNTRIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose and target audience</strong></td>
<td>To provide a focus for global action on TB in the countries where progress is most needed to achieve End TB Strategy and SDG targets and milestones, to help build and sustain national political commitment and funding in the countries with the highest burden in terms of absolute numbers or severity, and to promote global monitoring of progress in a well-defined set of countries.</td>
<td>To provide a focus for global action on HIV-associated TB in the countries where progress is most needed to achieve End TB Strategy, UNAIDS and SDG targets and milestones, to help build and sustain national political commitment and funding in the countries with the highest burden in terms of absolute numbers or severity, and to promote global monitoring of progress in a well-defined set of countries.</td>
<td>To provide a focus for global action on the MDR-TB crisis in the countries where progress is most needed to achieve End TB Strategy targets and milestones, to help build and sustain national political commitment and funding in the countries with the highest burden in terms of absolute numbers or severity, and to promote global monitoring of progress in a well-defined set of countries.</td>
</tr>
<tr>
<td><strong>Countries in the list</strong></td>
<td>The top 20 by estimated absolute number (in alphabetical order): Angola, Bangladesh, Brazil, China, DPR Korea, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, UR Tanzania, Viet Nam</td>
<td>The top 20 by estimated absolute number (in alphabetical order): Angola, Brazil, Cameroon, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Lesotho, Liberia, Namibia, Papua New Guinea, Sierra Leone, Zambia, Zimbabwe</td>
<td>The top 20 by estimated absolute number (in alphabetical order): Bangladesh, China, DPR Korea, DR Congo, Ethiopia, India, Kazakhstan, Kenya, Indonesia, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Ukraine, Uzbekistan, Viet Nam</td>
</tr>
<tr>
<td>% global total</td>
<td>84%</td>
<td>3.1%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Lifetime of list</strong></td>
<td>5 years (review criteria and included countries in June 2020).</td>
<td>5 years (review criteria and included countries in June 2020).</td>
<td>5 years (review criteria and included countries in June 2020).</td>
</tr>
</tbody>
</table>

DPR Korea, Democratic People’s Republic of Korea; DR Congo, Democratic Republic of the Congo; HIV, human immunodeficiency virus; MDR, multidrug resistant; SDG, Sustainable Development Goal; TB, tuberculosis; UNAIDS, Joint United Nations Programme on HIV/AIDS; UR Tanzania, United Republic of Tanzania; WHO, World Health Organization

End TB Strategy. In addition, the Global TB Programme has begun working with a pilot group of countries in the African Region on collection of data using this approach.

For the first time, this report includes chapters related to TB prevention (Chapter 5) and UHC and social protection (Chapter 6), reflecting the much greater prominence of these topics in the End TB Strategy compared with previous global TB strategies.

2.3 Lists of high-burden countries to be used by WHO during the period 2016–2020

During the period 1998 to 2015, the concept of an HBC became familiar and widely used in the context of TB. In 2015, three lists – for TB, TB/HIV and MDR-TB – were in use. The TB HBC list (22 countries) had remained unchanged since 2002, and the HBC lists for TB/HIV (41 countries) and MDR-TB (27 countries) had not been updated since 2009 and 2008, respectively. With 2015 marking the end of the MDGs and their replacement with the SDGs, and the last year of the Stop TB Strategy and its replacement with the...
End TB Strategy, it was an ideal time to revisit these three HBC lists.

Following a wide consultation process, WHO has defined three new HBC lists for the period 2016–2020: one for TB, one for MDR-TB and one for TB/HIV (Fig. 2.2, Table 2.2). Each list contains 30 countries (Table 2.2). These are defined as the top 20 in terms of absolute numbers of cases, plus the additional 10 countries that have the most severe burden in terms of incidence rates per capita, do not appear in the top 20 and meet a minimum threshold in terms of absolute numbers of incident cases (10 000 per year for TB, and 1000 per year for TB/HIV and MDR-TB). The lists were defined using the latest estimates of TB disease burden available in October 2015. Each list accounts for 87–92% of the global burden, with almost all of this accounted for by the top 20 countries in each list.

There is overlap among the three lists, but 48 countries appear in at least one list. The 14 countries that are in all three lists (shown in the central diamond in Fig. 2.2) are: Angola, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Papua New Guinea, South Africa, Thailand and Zimbabwe.

The 30 high TB burden countries are given particular attention in the main body of this report. Where estimates of disease burden and assessment of progress in the response are for TB/HIV and MDR-TB specifically, the countries in the TB/HIV and MDR-TB lists respectively are given particular attention. Annex 2 contains a one-page profile for each of the 30 high TB burden countries, with a clear demarcation between the 20 countries included on the basis of absolute numbers of incident cases and the 10 additional countries included on the basis of the incidence rate per capita.

As in the 2015 global TB report, data for all countries are included in Annex 4 and in WHO’s online global TB database. Country profiles for all countries (with the same content as those presented in Annex 2) are also available online.

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2 As explained in the last row of Table 2.2, the three lists have a lifetime of 5 years, and the countries included in each list and the criteria used to define each list will be reviewed in June 2020.
Chapter 3 :: TB disease burden

KEY FACTS AND MESSAGES

Global targets and milestones for reductions in the burden of TB disease in the period 2016–2035 have been set as part of the Sustainable Development Goals (SDGs) and WHO’s End TB Strategy.

The first milestones of the End TB Strategy, set for 2020, are a 35% reduction in the absolute number of TB deaths and a 20% reduction in the TB incidence rate, compared with levels in 2015. To reach these milestones, the TB incidence rate needs to be falling by 4–5% per year globally by 2020 and the proportion of people with TB who die from the disease (the case fatality ratio or CFR)* needs to be reduced to 10% globally by 2020.

A substantial acceleration in the current rate of progress in reducing the burden of TB disease, based on all elements of the End TB Strategy, is required to bring these milestones within reach.

Globally, the absolute number of TB deaths (excluding TB deaths among HIV-positive people) and the TB incidence rate have fallen since 2000. The number of TB deaths fell from 1.8 million in 2000 to 1.4 million in 2015. However, the global rate of decline in the TB incidence rate was only 1.5% from 2014 to 2015 and the CFR in 2015 was 17%. TB is one of the top 10 causes of death worldwide and caused more deaths than HIV in 2015.

Worldwide in 2015, there were an estimated 10.4 million incident TB cases. An estimated 62% of these cases were male, and 90% of cases were adults. Six countries accounted for 60% of the global total: India, Indonesia, China, Nigeria, Pakistan and South Africa. The rate of progress in these countries will have a major influence on whether or not the 2020 global milestones are achieved.

Estimates of the burden of TB disease in India have been revised substantially upwards for the period 2000–2015, compared with those published in previous reports. This follows accumulating evidence from surveys and routinely collected TB notification data that previous estimates of cases and deaths were too low. As the country with the highest burden of TB disease in the world, these revisions have had a major impact on the global estimates. The estimates for India are still considered as interim, pending a national TB prevalence survey scheduled for 2017/2018.

An estimated 11% of incident TB cases in 2015 were HIV-positive. The proportion was highest in countries in the WHO African Region, and exceeded 50% in parts of southern Africa. In addition to the 1.4 million TB deaths among HIV-negative people, there were 0.4 million deaths from TB among HIV-positive people* in 2015.

Variation in the CFR in 2015, from under 5% in a few countries to more than 20% in most countries in the WHO African Region, shows considerable inequalities among countries in access to TB diagnosis and treatment that need to be addressed. If everyone with TB had a timely diagnosis and access to high-quality treatment, the CFR would be low in all countries.

Following WHO guidance issued in May 2016, all cases of rifampicin-resistant TB (RR-TB), including those with multidrug-resistant TB (MDR-TB), should be treated with a second-line MDR-TB treatment regimen. Globally in 2015, there were an estimated 480 000 new cases of MDR-TB and an additional 100 000 people with rifampicin-resistant TB who were also newly eligible for MDR-TB treatment; India, China and the Russian Federation accounted for 45% of these cases.

Until national notification and vital registration systems (with standard coding of causes of death) of high coverage and quality are present in all countries, national TB prevalence surveys will continue to provide the best method for directly measuring the burden of TB disease and identifying actions required to reduce that burden in an important subset of countries. In recent years, there has been enormous progress in implementing such surveys, with 22 completed between 2009 and August 2016. In this report, estimates of TB incidence were derived from prevalence surveys for 20 countries with 62% of the world’s TB cases.

* The CFR can be approximated as the number of TB deaths divided by the number of incident cases in the same year.

* When an HIV-positive person dies from TB disease, the underlying cause is classified as HIV in the International Classification of Diseases system (ICD-10).
The burden of tuberculosis (TB) disease can be measured in terms of:

- **incidence** – the number of new and relapse cases of TB arising in a given time period, usually 1 year;
- **prevalence** – the number of cases of TB at a given point in time; and
- **mortality** – the number of deaths caused by TB in a given time period, usually 1 year.

Global targets and milestones for reductions in the burden of TB disease have been set as part of the Sustainable Development Goals (SDGs) and WHO’s End TB Strategy (Chapter 2). SDG3 includes a target to end the global TB epidemic by 2030, with TB incidence (per 100,000 population) defined as the indicator for measurement of progress. The 2030 targets set in the End TB Strategy are a 90% reduction in TB deaths and an 80% reduction in TB incidence, compared with levels in 2015. Targets for 2035 and milestones for 2020 and 2025 have also been defined (Table 3.1).

### TABLE 3.1
**Targets for percentage reductions in TB disease burden set in WHO’s End TB Strategy**

<table>
<thead>
<tr>
<th>INDICATORS</th>
<th>MILESTONES</th>
<th>TARGETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)</td>
<td>2020</td>
<td>2025</td>
</tr>
<tr>
<td>Percentage reduction in the absolute number of TB deaths (compared with 2015 baseline)</td>
<td>35</td>
<td>75</td>
</tr>
<tr>
<td>Percentage reduction in the TB incidence rate (compared with 2015 baseline)</td>
<td>20</td>
<td>50</td>
</tr>
</tbody>
</table>

This chapter is structured in six major sections. Section 3.1 and Section 3.2 present the latest WHO estimates of TB incidence and mortality between 2000 and 2015. These sections also highlight sources of data and actions needed to improve measurement of TB incidence and mortality. Section 3.3 focuses on the burden of drug-resistant TB, including the latest status of progress in global surveillance of resistance to anti-TB drugs and estimates of the incidence of multidrug-resistant TB (MDR-TB) and rifampicin-resistant TB (RR-TB). Section 3.4 discusses national TB prevalence surveys. Although TB prevalence is no longer an indicator for which a global target has been set, in many countries, national TB prevalence surveys still provide the best method for estimating the burden of TB disease and for planning actions needed to reduce that burden. In addition, results from national TB prevalence surveys can inform estimates of TB incidence and mortality, and thus contribute to monitoring of progress towards SDG and End TB Strategy targets. Finally, Section 3.5 and Section 3.6 cover disaggregated estimates of disease burden (TB incidence and mortality by age and sex), and what can be learned from disaggregated analysis (by age, sex and location) of TB surveillance and survey data. This is in line with the increasing emphasis on the importance of within-country disaggregation of key indicators in the SDGs and the End TB Strategy (Chapter 2).

WHO updates its estimates of the burden of TB disease annually, using the latest available data and analytical methods. Since 2006, concerted efforts have been made to improve the available data and methods used, under the umbrella of the WHO Global Task Force on TB Impact Measurement (Box 3.1). A summary of the main updates to available data and methods since the 2015 global TB report is provided in Box 3.2; further details for India are provided in Box 3.3.

### 3.1 TB incidence

#### 3.1.1 Methods to estimate TB incidence

TB incidence has never been measured at national level because this would require long-term studies among large cohorts (hundreds of thousands) of people, which would involve high costs and challenging logistics. Notifications of TB cases provide a good proxy indication of TB incidence in countries that have high-performance surveillance systems (e.g. with little underreporting of diagnosed cases), and in which the quality of and access to health care means that few cases are not diagnosed. In the large number of countries where these criteria are not yet met, better estimates of TB incidence can be obtained from an inventory study (i.e. a survey to quantify the level of underreporting of detected TB cases); also, if certain conditions are met, results from an inventory study can be combined with capture–recapture methods to estimate TB incidence. To date, such studies have been undertaken in only a few countries, but interest and implementation is growing (Box 3.4).

The ultimate goal is to directly measure TB incidence from TB notifications in all countries. This requires a combination of strengthened surveillance, better quantification of underreporting (i.e. the number of cases that are missed by surveillance systems) and universal access to health care. A TB surveillance checklist developed by the WHO Global Task Force on TB Impact Measurement (Box 3.1)

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2. This is in contrast to the eras of the Millennium Development Goals and Stop TB Strategy, when a target of halving prevalence between 1990 and 2015 was set.

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3. The online technical appendix is available at www.who.int/tb/data.
4. The updates can affect the entire time-series back to 2000. Therefore, estimates presented in this chapter for 2000–2014 supersede those of previous reports, and direct comparisons (e.g. between the 2014 estimates in this report and the 2014 estimates in the previous report) are not appropriate.
5. Inventory studies can be used to measure the number of cases that are diagnosed but not reported. For a guide to inventory studies, see World Health Organization. Assessing tuberculosis under-reporting through inventory studies. Geneva: WHO; 2012 (http://www.who.int/tb/publications/inventory_studies/en/, accessed 15 August 2016).
Progress to date

The WHO Global Task Force on TB Impact Measurement (hereafter referred to as the Task Force) was established in 2006 and is convened by the TB Monitoring and Evaluation unit of WHO’s Global TB Programme. Its aim was to ensure that WHO’s assessment of whether 2015 targets set in the context of the MDGs were achieved at global, regional and country levels was as rigorous, robust and consensus-based as possible. Three strategic areas of work were pursued:

- strengthening routine surveillance of TB cases (via national notification systems) and deaths (via national VR systems) in all countries;
- undertaking national TB prevalence surveys in 22 global focus countries; and
- periodically reviewing methods used to produce TB disease burden estimates.

Notification data are consistently reported to WHO by about 200 countries and territories each year. In 2015, direct measurements of TB mortality from national or sample VR systems were available for 128 countries. Between 2009 and the end of 2015, a total of 19 national TB prevalence surveys were completed. When surveys in the Philippines and Viet Nam in 2007 are included, 16 of the 22 global focus countries had completed a survey according to screening and diagnostic methods recommended by WHO by the end of 2015.

Comprehensive reviews of methods used by WHO to produce estimates of TB incidence, prevalence and mortality were undertaken between June 2008 and October 2010, and in a meeting of the Task Force dedicated to this topic in April 2015. WHO published its assessment of whether 2015 global TB targets for reductions in TB incidence, prevalence and mortality were achieved in its 2015 global TB report, using the methods agreed in April 2015.

Looking forward: mandate and strategic areas of work, 2016–2020

In the context of a new era of SDGs and WHO’s End TB Strategy, the Task Force met in April 2016 to review and reshape its mandate and strategic areas of work for the post-2015 era. An updated mandate and five strategic areas of work for the period 2016–2020 were agreed.7

The mandate was defined as follows:

- To ensure that assessments of progress towards End TB Strategy and SDG targets and milestones at global, regional and country levels are as rigorous, robust and consensus-based as possible.
- To guide, promote and support the analysis and use of TB data for policy, planning and programmatic action.

The five strategic areas of work are as follows:

1. Strengthening national notification systems for direct measurement of TB cases, including drug-resistant TB and HIV-associated TB specifically.
2. Strengthening national VR systems for direct measurement of TB deaths.
3. Priority studies to periodically measure TB disease burden, including:
   - national TB prevalence surveys
   - drug-resistance surveys
   - mortality surveys
   - surveys of costs faced by TB patients and their households.
4. Periodic review of methods used by WHO to estimate the burden of TB disease and latent TB infection.
5. Analysis and use of TB data at country level, including:
   - disaggregated analyses (e.g. by age, sex, location) to assess inequalities and equity
   - projections of disease burden
   - guidance, tools and capacity building.

The SDG and End TB Strategy targets and milestones referred to in the mandate are the targets (2030, 2035) and milestones (2020, 2025) set for the three high-level indicators: that is, TB incidence, the number of TB deaths and the percentage of TB-affected households that face catastrophic costs as a result of TB disease (Chapter 2).

Strategic areas of work 1–3 are focused on direct measurement of TB disease burden (epidemiological and, in the case of cost surveys, economic). The underlying principle for the Task Force’s work since 2006 has been that estimates of the level of and trends in disease burden should be based on direct measurements from routine surveillance and surveys as much as possible, as opposed to indirect estimates based on modelling and expert opinion. However, strategic area of work 4 does recognize that indirect estimates will continue to be required until all countries have the surveillance systems or the periodic studies required to provide direct measurements. Strategic area of work 5 recognizes the importance of analysing and using TB data at country level (as well as generating data, as in areas of work 1–3), including the disaggregated analyses that are now given much greater attention in the SDGs and End TB Strategy.

In the next 5 years, the top priorities for the Task Force are strengthening of national notification and VR systems as the basis for direct measurement of TB incidence and TB mortality.

Further details about the work of the Task Force are available online; an up-to-date summary is provided in the latest brochure about its work.8
Updates in this report

1. Interim update for India
Estimates for India have been updated following an accumulating body of evidence that indicated that previously published estimates were too low. The updated estimates are interim in nature. A more definitive assessment will follow the completion of a national TB prevalence survey scheduled for 2017/2018. Further details are provided in Box 3.3.

2. New data from national TB prevalence surveys
Between October 2014 and August 2015, final results from surveys in Mongolia and Uganda became available. The post-survey estimate of TB prevalence in Uganda was consistent with pre-survey estimates, but was more precise and had values located towards the upper end of the previously published uncertainty interval. In Mongolia, TB prevalence was higher than anticipated. More details are provided in Section 3.4.

3. Newly reported data and updated estimates from other agencies
New VR data were reported to WHO between mid-2015 and mid-2016, and some countries made corrections to historical data. Updated estimates of the burden of disease caused by HIV were obtained from UNAIDS in July 2016. In most instances, any resulting changes to TB burden estimates were well within the uncertainty intervals of previously published estimates, and trends were generally consistent.

For South Africa, estimates of TB mortality (HIV-negative) were based on estimates from the Institute of Health Metrics and Evaluation (IHME), Washington University, USA; these estimates use data from the national VR system, adjusted for widespread miscoding of deaths caused by HIV and TB. For India, estimates of TB mortality (HIV-negative) were also based on estimates from IHME, following the Institute’s extensive analysis of available mortality data (see also Box 3.3).

4. Deaths due to TB sequelae
For the first time in 2016, deaths attributed to TB sequelae (ICD-10 codes B90.*) are included in HIV-negative TB mortality estimates for countries reporting VR data to WHO. The proportion of overall TB deaths that were classified as deaths from TB sequelae varies widely between countries (Fig. B3.2.1) as a result of variation in certification practices (i.e. what is written on death certificates) or coding (i.e. which code is selected).

5. In-depth epidemiological reviews at country level
A regional workshop on TB epidemiology and TB mortality was held in Lima, Peru in June 2016. Methods to estimate TB incidence were reviewed and altered in most countries, shifting to the high-income method based on a larger standard adjustment factor (using a factor of [1, 1.5] except in Brazil, where the standard factor already used for high-income countries was applied). A national TB epidemiology workshop was held in China in April 2016, to review options for estimating TB disease burden. Estimates of TB incidence in 2009–2015 are now based on notifications adjusted by a standard factor to account for underreporting and underdiagnosis, with the standard adjustment [1, 1.3] based on that already used for high-income countries (see also Section 3.1). Mortality estimates are derived from the sample VR system, as before.

:: FIG. B3.2.1
Deaths from TB sequelae as a proportion of the total number of reported TB deaths, countries reporting national VR data (using the most recent year of data reported to WHO)
6. Indirect prevalence estimates are no longer presented

National TB prevalence surveys will continue to provide the best method for measuring the burden of TB disease and related assessment of actions needed to reduce that burden in a large number of countries – specifically, those with a high burden of TB that do not yet have health, national notification and VR systems of the quality and coverage required to provide reliable and routine measurements of the number of TB cases and deaths. Results from these surveys will continue to be featured in global TB reports. However, indirect estimates of prevalence for other countries are no longer presented. Prevalence is not an indicator in the SDGs or a high-level indicator of the End TB Strategy, and no global target has been set (in contrast to the era of the MDGs and Stop TB Strategy, when a target of halving prevalence between 1990 and 2015 was set). Furthermore, indirect estimates of prevalence suffer from considerable uncertainty, because they are derived from estimates of incidence and assumptions about disease duration.

7. Time series of TB burden estimates start with the year 2000

Series of TB estimates published in this report start with the year 2000. In previous reports, estimates started in 1990, because this was the baseline for the 2015 global targets set in the context of the MDGs. TB data for the period 1990–2000 were of relatively poor quality in many countries, because standardized systems for recording and reporting cases were often introduced only after the mid-1990s, in association with the introduction of the DOTS strategy (WHO’s recommended global TB strategy from the mid-1990s until the end of 2005). The quality and coverage of TB data since 2000 are comparatively much improved, and estimates are generally more robust.

8. Estimates of the burden of drug-resistant TB

Previous WHO global TB reports have focused on the burden of MDR-TB. In this report, estimates are of the burden of RR-TB (TB resistant to rifampicin, with or without resistance to other drugs) including MDR-TB, and are referred to as MDR/RR-TB. This update is because the latest WHO guidance on treatment of drug-resistant TB (an update issued in May 2016, see Chapter 4, Box 4.3) recommends that all people with RR-TB (not only those with MDR-TB) should be treated with an MDR-TB treatment regimen. Estimates of the burden of MDR/RR-TB are thus needed to assess progress in detection and treatment coverage for drug-resistant TB. Global and national estimates of the incidence of MDR/RR-TB are presented in this chapter; in addition, Chapter 4 includes estimates of the number of cases of MDR/RR-TB among notified cases of pulmonary TB (i.e. the number of cases that could be detected if all notified TB cases were tested for drug resistance). Methods used to produce the estimates of the incidence of MDR/RR-TB featured in this report are those agreed following an expert review during the April 2016 meeting of the WHO Global Task Force on TB Impact Measurement.\(^a\)

9. Country-level estimates of TB incidence disaggregated by age and sex

In line with the SDG and End TB Strategy requirements for higher levels of data granularity and corresponding estimates, country-level estimates of TB incidence disaggregated by age (children and adults) and sex are shown (see Annex 2 and 3). Estimates of TB incidence in children (aged <15 years) are based on methods previously used at a global level, in which estimates based on case notifications adjusted for underdetection and underreporting\(^a\) are combined with estimates derived from dynamic modelling.\(^b\)

Updates anticipated in the near future

Updates to estimates of disease burden are expected towards the end of 2016 or in early 2017 for Bangladesh, Kenya and the Philippines, following the completion of national TB prevalence surveys. Estimates of TB incidence in Indonesia, the Philippines, Thailand and Viet Nam may be updated following the implementation of inventory studies to measure underreporting of detected TB cases. Estimates of TB burden in India will be further updated once results from the national TB prevalence survey are available. Updates to childhood TB mortality (primarily for the 0-14 year age group and, where possible, further disaggregated for those aged 0–4 and 5–14 years) are expected by early 2017, based on a systematic review and meta-analysis to inform CFRs for children\(^c\) and a mathematical model estimating TB mortality in children as a function of TB incidence and CFRs.\(^d\)


\(^c\) For further details, please see Background Document 3b prepared for the April 2016 meeting of the Task Force, available at www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/tf6_background_3b_drtn_burden.pdf?ua=1.


\(^f\) Jenkins H et al. Mortality among children diagnosed with tuberculosis: Systematic review and meta-analysis. Submitted for publication.

The updated estimates of TB disease burden in India published in the 2011–2015 global TB reports were based on the outcomes of a national consensus workshop held in Delhi in April 2011. This report includes estimates for India that have been revised substantially upwards compared with those published in 2011–2015, following accumulating evidence that the TB disease burden in India is higher than was estimated at that time.

The revised estimates of TB incidence (absolute numbers) are based on extrapolation of the results from a prevalence survey in one state (Gujarat). This survey used methods recommended by WHO and is the largest as well as the only state-wide prevalence survey implemented in India to date. It was assumed that the national prevalence of TB disease is the same as the prevalence in Gujarat, with incidence then estimated using a standard methodological approach recently reviewed by the WHO Global Task Force on TB Impact Measurement.\(^1\) The trend in TB incidence is estimated as in global reports published 2011–2015; that is, using results from repeat tuberculin surveys (2000, 2010) and (to a lesser extent) trends in TB notifications in the districts where the Revised National TB Control Programme first implemented the DOTS strategy.

The revised estimates of TB mortality are derived from those published by IHME,\(^2\) after adjustment for differences between WHO and IHME estimates of the total number of deaths each year.

These updated estimates of TB burden in India are considered interim estimates, pending results from a national TB prevalence survey that is scheduled to start in 2017 (see also Section 3.4).

The revised estimates, and how they compare with those published in the 2015 global TB report, can be summarized as follows:

- The updated estimate of incidence (new TB cases per year) is 2.8 million cases in 2015 (217 per 100 000 population), and 2.9 million (223 per 100 000 population) in 2014. These figures can be compared with notifications of 1.7 million new and relapse cases in 2015 (127 per 100 000 population) and 1.6 million new and relapse cases in 2014 (124 per 100 000 population). These figures suggest that 56% of incident cases were officially reported in 2014 and 59% in 2015. In the 2015 global TB report, the estimate for 2014 was that there were 2.2 million incident cases (167 per 100 000 population), with an estimated 74% of incident cases officially reported.

- The updated estimate of the number of TB deaths (excluding those in HIV-positive people, which are classified as deaths due to HIV/AIDS in ICD-10) is 478 000 in 2015 (36 per 100 000 population), and 483 000 (37 per 100 000 population) in 2014. In the 2015 global TB report, the estimate for 2014 was 220 000 (17 per 100 000 population).

- Estimated trends in TB incidence and mortality remain similar to those published in previous years, with incidence falling by 2% per year over 2000–2015 and mortality falling by 3.3% per year over the same period.

The six sources of evidence that the burden of TB is higher than estimated in April 2011 are summarized below.

1. **Household survey in 30 districts of numbers of people on TB treatment, 2011**

Starting in 2011, a TB project that aimed to increase civil society’s support to the NTP in India and to engage communities and community-based care providers was implemented in 374 out of 650 districts.\(^1\) The 374 districts were selected based on suspected low TB case detection or limited access of populations to health services. Funding for the project was from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund).

In a sample of 30 of the 374 districts, the number of people on TB treatment based on self-reporting was assessed using a dataset compiled as part of a survey of knowledge, attitudes and practices conducted from January to March 2011. Of the self-reported cases, 54% had not been officially reported to national authorities. The number of undetected cases could not be assessed because of the study design. For comparison, the estimate published in the 2015 global TB report was that 59% of incident cases were officially reported in 2010 (with the gap of 41% including both unreported and undetected cases).

2. **Results from a state-wide prevalence survey in Gujarat state**

In 2011, a prevalence survey was conducted in Gujarat. This was the country’s first state-wide survey (other surveys have been conducted in districts that were not nationally representative). Results were shared with WHO in 2015, and indicated a prevalence (adjusted for all ages and all forms of TB) of 390 cases per 100 000 population. This is much higher than the national estimate published by WHO in the 2015 global TB report of 250 prevalent cases per 100 000 population. Gujarat is among the wealthiest states in India, and given the link between overall levels of income and the burden of TB disease it seems unlikely that TB prevalence in Gujarat would be higher than the national average.

3. **A district level household and facility survey (DLHS-4)**

A survey in 2012–2013 estimated prevalence based on interview screening at 592 cases per 100 000. However, this method for estimating prevalence is not recommended in the WHO handbook on TB prevalence surveys.
4. **A study of sales of anti-TB drugs, 2014**

A study of sales of anti-TB drugs in 2014 was published in 2016. The study indicated that there were 17.8 million patient-months of TB treatment in the private sector, twice as many as in the public sector. The authors noted that if 40–60% of private-sector TB diagnoses are correct, and if private-sector TB treatment lasts on average 2–6 months, then about 2.2 million (range 1.2 million to 5.3 million) TB cases were treated in the private sector in 2014. This is 2–3 times higher than the level assumed when the April 2011 workshop on TB disease burden estimates (mentioned above) was held.

5. **A large increase in national case notifications in 2013–2015**

India implemented a policy of mandatory TB notification in 2012 and has also rolled out a national web-based reporting system since 2012. In 2014, the number of notified cases increased by 29% compared with 2013, and the number of notified cases in 2015 was 34% higher than the level of 2013. Most of the increase is related to improved coverage of notifications from the private sector in a small number of districts.

6. **Analyses of TB mortality by IHME**

IHME has used a large body of cause-of-death data from VR and verbal autopsy surveys, including data that are not yet accessible to WHO, to estimate TB mortality in India. The estimated number of TB deaths is much higher than previously published WHO estimates.

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Global Tuberculosis Report 2016 defines the standards that need to be met for notification data to provide a direct measure of TB incidence. By August 2016, a total of 42 countries, including 19 of the 30 high TB burden countries (listed in Table 3.2) had completed the checklist, often in association with a TB epidemiological review or regional workshop focused on analysis of TB data (Fig. 3.1).

Methods currently used by WHO to estimate TB incidence can be grouped into four major categories, as follows (Fig. 3.2):

1. **Case notification data combined with expert opinion about case-detection gaps.** Expert opinion, elicited in regional workshops or country missions, is used to estimate levels of underreporting and underdiagnosis. Trends are estimated through mortality data, surveys of the annual risk of infection or exponential interpolation using estimates of case-detection gaps for 3 years. In this report, this method is used for 74 countries that accounted for 22% of the estimated global number of incident cases in 2015.

2. **Results from TB prevalence surveys.** Incidence is estimated using prevalence survey results and estimates of the duration of disease, with the latter derived from a model that accounts for the impact of HIV co-infection on the distribution of disease duration. This method is used for 20 countries, 19 of which have national survey data and one – India – that has a survey in one state. The 20 countries accounted for 62% of the estimated global number of incident cases in 2015.

3. **Notifications in high-income countries adjusted by a standard factor to account for underreporting and underdiagnosis.** This method is used for 118 countries: all high-income countries except the Netherlands and the United Kingdom, plus selected upper-middle income countries with low levels of underreporting, including Brazil and China. For three countries (France, Republic of Korea and Turkey) the adjustment was country specific, based on results from studies of underreporting. These 118 countries accounted for 15.5% of the estimated global number of incident cases in 2015.

4. **Results from inventory studies and capture-recapture analysis.** This method is used for five countries: Egypt, Iraq, the Netherlands, the United Kingdom and Yemen. These countries accounted for 0.5% of the estimated global number of incident cases in 2015.

Further details about these methods are provided in the online technical appendix and in background documents prepared for the global review of methods used to produce TB burden estimates that was held in April 2015 (Box 3.1).
The accurate understanding and measurement of TB incidence, one of the high-level indicators consistently used by the global health community since 2000, is pivotal to monitoring progress against international targets set for TB in the End TB Strategy and the SDGs, and for assessing whether investments in TB care and prevention actually work. Although the level of and trends in TB incidence could be directly measured through population cohort studies, national cohort studies are too expensive and impractical to implement. In settings with state-of-the-art routine surveillance systems where most, if not all, new TB cases are diagnosed and registered, TB cases notified to the NTP provide a good proxy for TB incidence. More often than not, however, case-detection gaps plague national TB surveillance systems at different stages in the patient cascade, including gaps in diagnosis, treatment and reporting. TB inventory studies are a customized and more cost-effective alternative to population cohort studies that could inform the extent of such gaps. TB inventory studies have two broad study objectives, one involving the direct measurement of TB underreporting and the other, under certain conditions, the estimation of TB incidence through capture-recapture analysis.

There has been growing interest in and implementation of national inventory studies to measure TB underreporting in the past 10 years (Fig. B3.4.1) – often in combination with capture-recapture analysis – in countries including the Netherlands, the United Kingdom, French Guiana, Egypt, Yemen, Iraq, Pakistan and Kenya. Hypothesis-generating investigations to assess the level of TB case-detection gaps were also completed in India (cross-sectional survey of households), Indonesia and Viet Nam (nested within a national prevalence survey among adults). Based on these studies, the level of TB underreporting found was context-dependent, and ranged from about 15% in European countries, 20% in Africa and 30% in the WHO Eastern Mediterranean Region, to 50% in countries in Asia with a large private sector. These data have all informed national estimates of TB disease burden reported by WHO. Results from TB inventory studies provide the platform and evidence to make programmatic changes to better address the TB epidemic. The European Centre for Disease Prevention and Control acknowledges the value of inventory studies for providing evidence about the performance of surveillance systems in Europe, and UNITAID and the Global Fund are already supporting the implementation of national TB inventory studies in Asia, including some studies with a particular focus on children.

 Strengthening national TB surveillance systems and the data they produce is the only credible way to ensure the robust and routine monitoring of progress towards global targets for TB. Inventory studies are an important tool, one of the few available today, for achieving that goal for TB surveillance. As countries begin working towards the new TB incidence targets set within the SDGs and the End TB Strategy, increased commitment from NTPs and funding agencies to conducting and fund TB inventory studies is required.

**Box 3.4**

Inventory studies to measure the underreporting of detected TB cases: progress to date

The accurate understanding and measurement of TB incidence, one of the high-level indicators consistently used by the global health community since 2000, is pivotal to monitoring progress against international targets set for TB in the End TB Strategy and the SDGs, and for assessing whether investments in TB care and prevention actually work. Although the level of and trends in TB incidence could be directly measured through population cohort studies, national cohort studies are too expensive and impractical to implement. In settings with state-of-the-art routine surveillance systems where most, if not all, new TB cases are diagnosed and registered, TB cases notified to the NTP provide a good proxy for TB incidence. More often than not, however, case-detection gaps plague national TB surveillance systems at different stages in the patient cascade, including gaps in diagnosis, treatment and reporting. TB inventory studies are a customized and more cost-effective alternative to population cohort studies that could inform the extent of such gaps. TB inventory studies have two broad study objectives, one involving the direct measurement of TB underreporting and the other, under certain conditions, the estimation of TB incidence through capture-recapture analysis.

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**FIG. B3.4.1**

Countries in which inventory studies of the underreporting of detected TB cases have been implemented since 2000 (status in August 2016)*

* Pakistan is currently undertaking a second inventory study focussing on children with TB.
* Nigeria is planning to undertake a subnational level study (in metropolitan Lagos).

[Map of countries]
**FIG. 3.1**

**Strengthening national TB surveillance (status in August 2016)**

**Countries in which a checklist of standards and benchmarks has been completed since January 2013**

**Countries in which an epidemiological review has been undertaken since July 2012**

**Countries covered by a regional or country-specific workshop focused on analysis and use of TB data since October 2015**
3.1.2 Estimates of TB incidence in 2015

Globally in 2015, there were an estimated 10.4 million incident cases of TB (range, 8.7 million to 12.2 million),¹ equivalent to 142 cases per 100 000 population (estimates of absolute numbers are shown in Table 3.2 and estimates of rates per capita are shown in Table 3.3). As explained in Box 3.2, estimates of TB incidence have been revised upwards for the period 2000–2015, compared with those published in the 2015 global TB report. This follows accumulating evidence that the burden of TB disease in India is considerably higher than previously estimated (Box 3.3), and more minor upward revisions for the Democratic People’s Republic of Korea and the Philippines. The updated estimates for India should be considered interim in nature, pending a more definitive assessment that will follow completion of a national TB prevalence survey, which is scheduled to start in 2017.

Most of the estimated number of cases in 2015 occurred in Asia (61%)² and the WHO African Region (26%); smaller proportions of cases occurred in the Eastern Mediterranean Region (7%), the European Region (3%) and the Region of the Americas (3%). The 30 high TB burden countries³ accounted for 87% of all estimated incident cases worldwide. The six countries that stood out as having the largest number of incident cases in 2015 were (in descending order) India, Indonesia, China, Nigeria, Pakistan and South Africa (combined, 60% of the global total). Of these, China, India and Indonesia alone accounted for 45% of global cases in 2015.

The annual number of incident TB cases relative to population size (the incidence rate) varied widely among countries in 2015, from under 10 per 100 000 population in most high-income countries to 150–300 in most of the 30 high TB burden countries (Fig. 3.3), and above 500 in a few countries including Lesotho, Mozambique and South Africa (Table 3.3).

An estimated 11% (range, 9–14%) of the incident TB cases in 2015 were among people living with HIV (Table 3.2, Table 3.3). The proportion of TB cases coinfected with HIV was highest in countries in the WHO African Region, and exceeded 50% in parts of southern Africa (Fig. 3.4).

Estimates of the incidence of zoonotic TB are shown in Box 3.5.

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¹ In the first method, case notification data are combined with expert opinion about case detection gaps (under-reporting and under-diagnosis), and trends are estimated using either mortality data, repeat surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for three years. For all high-income countries except the Netherlands and the United Kingdom, notifications are adjusted by a standard amount or measure of under-reporting from inventory studies, to account for case detection gaps. In India, results from a subnational prevalence survey for the state of Gujarat were used. For further details about all four methods, see text.

² Here and elsewhere in the report, “Range” refers to the 95% uncertainty interval.

³ These countries are listed in Table 3.2 and Table 3.3. For an explanation of how the list of 30 high TB burden countries was defined, see Chapter 2.
### Table 3.2
Estimated epidemiological burden of TB in 2015 for 30 high TB burden countries, WHO regions and globally.
Numbers in thousands.  

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Population</th>
<th>HIV-NEGATIVE TB MORTALITY</th>
<th>HIV-POSITIVE TB MORTALITY</th>
<th>TOTAL TB INCIDENCE</th>
<th>HIV-POSITIVE TB INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Best Estimate</td>
<td>Uncertainty Interval</td>
<td>Best Estimate</td>
<td>Uncertainty Interval</td>
<td>Best Estimate</td>
</tr>
<tr>
<td>Angola</td>
<td>25 000</td>
<td>11</td>
<td>6.6–17</td>
<td>7.2</td>
<td>1.6–17</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>161 000</td>
<td>73</td>
<td>43–110</td>
<td>0.23</td>
<td>0.19–0.29</td>
</tr>
<tr>
<td>Brazil</td>
<td>208 000</td>
<td>5.5</td>
<td>5.2–5.9</td>
<td>2.2</td>
<td>1.2–3.6</td>
</tr>
<tr>
<td>Cambodia</td>
<td>15 600</td>
<td>8.6</td>
<td>6.1–12</td>
<td>0.44</td>
<td>0.19–0.79</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>4 900</td>
<td>2.2</td>
<td>1.3–3.4</td>
<td>2.7</td>
<td>1.0–5.3</td>
</tr>
<tr>
<td>China</td>
<td>1 380 000</td>
<td>35</td>
<td>34–37</td>
<td>2.6</td>
<td>1.2–4.5</td>
</tr>
<tr>
<td>Congo</td>
<td>4 620</td>
<td>2.3</td>
<td>1.3–3.5</td>
<td>2.4</td>
<td>2.0–2.9</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>25 200</td>
<td>15</td>
<td>10–22</td>
<td>0.04</td>
<td>0.02–0.06</td>
</tr>
<tr>
<td>DR Congo</td>
<td>77 300</td>
<td>51</td>
<td>30–77</td>
<td>16</td>
<td>13–20</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>99 400</td>
<td>25</td>
<td>15–38</td>
<td>3.9</td>
<td>1.6–7.3</td>
</tr>
<tr>
<td>India</td>
<td>1 310 000</td>
<td>480</td>
<td>380–590</td>
<td>37</td>
<td>21–57</td>
</tr>
<tr>
<td>Indonesia</td>
<td>258 000</td>
<td>100</td>
<td>67–150</td>
<td>26</td>
<td>20–34</td>
</tr>
<tr>
<td>Kenya</td>
<td>46 100</td>
<td>9</td>
<td>6.1–12</td>
<td>7.2</td>
<td>0.71–21</td>
</tr>
<tr>
<td>Lesotho</td>
<td>2 140</td>
<td>1.2</td>
<td>0.63–1.9</td>
<td>4.8</td>
<td>3.0–7.0</td>
</tr>
<tr>
<td>Liberia</td>
<td>4 500</td>
<td>3.2</td>
<td>1.9–4.8</td>
<td>0.84</td>
<td>0.70–1.0</td>
</tr>
<tr>
<td>Mozambique</td>
<td>28 000</td>
<td>21</td>
<td>12–32</td>
<td>34</td>
<td>21–50</td>
</tr>
<tr>
<td>Myanmar</td>
<td>53 900</td>
<td>27</td>
<td>16–40</td>
<td>4.8</td>
<td>3.5–6.5</td>
</tr>
<tr>
<td>Namibia</td>
<td>2 460</td>
<td>0.78</td>
<td>0.51–1.1</td>
<td>0.88</td>
<td>0.06–2.8</td>
</tr>
<tr>
<td>Nigeria</td>
<td>182 000</td>
<td>180</td>
<td>96–290</td>
<td>57</td>
<td>43–74</td>
</tr>
<tr>
<td>Pakistan</td>
<td>189 000</td>
<td>44</td>
<td>9.3–110</td>
<td>1.6</td>
<td>1.1–2.1</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>7 620</td>
<td>3.1</td>
<td>1.8–4.6</td>
<td>0.67</td>
<td>0.40–1.0</td>
</tr>
<tr>
<td>Philippines</td>
<td>101 000</td>
<td>14</td>
<td>8.8–19</td>
<td>0.44</td>
<td>0.24–0.70</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>143 000</td>
<td>15</td>
<td>15–16</td>
<td>1.5</td>
<td>&lt;0.01–7.4</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>6 450</td>
<td>3.3</td>
<td>1.9–4.9</td>
<td>0.82</td>
<td>0.40–1.4</td>
</tr>
<tr>
<td>South Africa</td>
<td>54 500</td>
<td>25</td>
<td>21–29</td>
<td>73</td>
<td>27–140</td>
</tr>
<tr>
<td>Thailand</td>
<td>68 000</td>
<td>8.4</td>
<td>6.9–10</td>
<td>5.4</td>
<td>3.3–8.1</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>53 500</td>
<td>30</td>
<td>13–53</td>
<td>25</td>
<td>16–35</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>93 400</td>
<td>16</td>
<td>11–22</td>
<td>1.1</td>
<td>0.20–2.7</td>
</tr>
<tr>
<td>Zambia</td>
<td>16 200</td>
<td>5</td>
<td>2.9–7.7</td>
<td>12</td>
<td>6.9–20</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>15 600</td>
<td>1.7</td>
<td>0.99–2.5</td>
<td>6.3</td>
<td>2.2–13</td>
</tr>
<tr>
<td><strong>High TB burden countries</strong></td>
<td>4 630 000</td>
<td>1200</td>
<td>1100–1400</td>
<td>340</td>
<td>280–410</td>
</tr>
<tr>
<td>Africa</td>
<td>989 000</td>
<td>450</td>
<td>350–560</td>
<td>300</td>
<td>230–360</td>
</tr>
<tr>
<td>The Americas</td>
<td>991 000</td>
<td>19</td>
<td>17–20</td>
<td>5.9</td>
<td>4.2–7.9</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>648 000</td>
<td>80</td>
<td>38–140</td>
<td>3</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Europe</td>
<td>910 000</td>
<td>32</td>
<td>31–33</td>
<td>4.9</td>
<td>1.5–10</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>1 930 000</td>
<td>710</td>
<td>600–830</td>
<td>74</td>
<td>56–95</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1 860 000</td>
<td>89</td>
<td>81–98</td>
<td>5.7</td>
<td>3.8–8.1</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>7 320 000</td>
<td>1400</td>
<td>1200–1600</td>
<td>390</td>
<td>320–460</td>
</tr>
</tbody>
</table>

*a* Numbers for mortality shown to two significant figures. Numbers for incidence shown to two significant figures if under 100 and to three significant figures otherwise.

*b* Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.

*c* Estimates of TB incidence and mortality for Bangladesh will be reviewed once final results from the 2015/2016 national TB prevalence survey are available.

*d* Estimates of incidence and mortality for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.
### TABLE 3.3

Estimated epidemiological burden of TB in 2015 for 30 high TB burden countries, WHO regions and globally. Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval. Rates per 100 000 population except where indicated.\(^{a}\)

<table>
<thead>
<tr>
<th>HIV-NEGATIVE TB MORTALITY</th>
<th>HIV-POSITIVE TB MORTALITY</th>
<th>TOTAL TB INCIDENCE</th>
<th>HIV PREVALENCE IN INCIDENT TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
</tr>
<tr>
<td><strong>High TB burden countries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angola</td>
<td>45</td>
<td>27–67</td>
<td>29</td>
</tr>
<tr>
<td>Bangladesh(^{b})</td>
<td>45</td>
<td>27–68</td>
<td>0.14</td>
</tr>
<tr>
<td>Brazil</td>
<td>2.7</td>
<td>2.5–2.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Cambodia</td>
<td>55</td>
<td>39–74</td>
<td>2.8</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>45</td>
<td>26–70</td>
<td>55</td>
</tr>
<tr>
<td>China</td>
<td>2.6</td>
<td>2.5–2.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Congo</td>
<td>49</td>
<td>29–75</td>
<td>53</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>61</td>
<td>40–87</td>
<td>0.15</td>
</tr>
<tr>
<td>DR Congo</td>
<td>66</td>
<td>39–99</td>
<td>21</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>26</td>
<td>15–38</td>
<td>4.0</td>
</tr>
<tr>
<td>India(^{a})</td>
<td>32</td>
<td>29–35</td>
<td>2.8</td>
</tr>
<tr>
<td>Indonesia</td>
<td>40</td>
<td>26–57</td>
<td>10</td>
</tr>
<tr>
<td>Kenya</td>
<td>20</td>
<td>13–27</td>
<td>16</td>
</tr>
<tr>
<td>Lesotho</td>
<td>55</td>
<td>29–89</td>
<td>223</td>
</tr>
<tr>
<td>Liberia</td>
<td>70</td>
<td>41–107</td>
<td>19</td>
</tr>
<tr>
<td>Mozambique</td>
<td>74</td>
<td>43–115</td>
<td>120</td>
</tr>
<tr>
<td>Myanmar</td>
<td>49</td>
<td>30–74</td>
<td>9.0</td>
</tr>
<tr>
<td>Namibia</td>
<td>32</td>
<td>21–45</td>
<td>36</td>
</tr>
<tr>
<td>Nigeria</td>
<td>99</td>
<td>53–160</td>
<td>31</td>
</tr>
<tr>
<td>Pakistan</td>
<td>23</td>
<td>4.9–56</td>
<td>0.83</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>41</td>
<td>24–61</td>
<td>8.8</td>
</tr>
<tr>
<td>Philippines</td>
<td>13</td>
<td>8.7–19</td>
<td>0.44</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>11</td>
<td>10–11</td>
<td>1.0</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>51</td>
<td>30–76</td>
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<tr>
<td>South Africa</td>
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<td>39–50</td>
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<tr>
<td>Thailand</td>
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<td>10–15</td>
<td>8.0</td>
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<td>12–23</td>
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<td>Zambia</td>
<td>31</td>
<td>18–47</td>
<td>77</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>11</td>
<td>6.3–16</td>
<td>40</td>
</tr>
<tr>
<td>Africa</td>
<td>45</td>
<td>35–57</td>
<td>30</td>
</tr>
<tr>
<td>The Americas</td>
<td>1.9</td>
<td>1.8–2.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>12</td>
<td>5.8–21</td>
<td>0.46</td>
</tr>
<tr>
<td>Europe</td>
<td>3.5</td>
<td>3.4–3.6</td>
<td>0.54</td>
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<tr>
<td>South-East Asia</td>
<td>37</td>
<td>31–43</td>
<td>3.9</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>4.8</td>
<td>4.4–5.3</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td><strong>19</strong></td>
<td><strong>17–21</strong></td>
<td><strong>5.3</strong></td>
</tr>
</tbody>
</table>

\(^{a}\) Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.

\(^{b}\) Estimates of TB incidence and mortality for Bangladesh will be reviewed once final results from the 2015/2016 national TB prevalence survey are available.

\(^{c}\) Estimates of TB incidence and mortality for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.
**FIG. 3.3**
Estimated TB incidence rates, 2015

**FIG. 3.4**
Estimated HIV prevalence in new and relapse TB cases, 2015
Mycobacterium bovis is the causal agent of bovine TB in cattle and zoonotic TB in people. Bovine TB has a major impact on livestock productivity, and on the livelihoods of poor and marginalised communities. The most common route of transmission to people is through the consumption of unpasteurized dairy products.

In 2015, there were an estimated 149,000 cases of zoonotic TB (Table B3.5.1). This was calculated by applying the regional proportions of all TB cases that are estimated to be caused by M. bovis to estimates of TB incidence in 2015. A standard deviation of 50% relative to the best estimate of each regional proportion was assumed when propagating uncertainty. Given the absence of routine reporting in most countries where bovine TB is endemic, these proportions were drawn from scientific studies that lack regional representativeness. As a result, estimates have a large uncertainty range. Mortality (excluding TB deaths in HIV-positive people) was similarly estimated based on the same proportions, but this time was applied to aggregated estimates of TB mortality by WHO region, and reduced by a factor of 20% to account for a higher proportion of extrapulmonary TB cases among those with M. bovis, and associated lower CFR.

There is a need to strengthen surveillance of zoonotic TB to better quantify the burden of disease. One of the major barriers for diagnosis is that the most commonly used laboratory procedures do not differentiate the M. tuberculosis complex into the species of M. bovis and M. tuberculosis. Zoonotic TB also presents a treatment challenge. It more often occurs in extrapulmonary sites and is inherently resistant to pyrazinamide, one of the drugs in the standard first-line anti-TB treatment regimen.

In the context of WHO’s End TB Strategy, which calls for diagnosis and treatment of every TB case, zoonotic TB must be better addressed. This requires a holistic approach that links the human and animal health sectors to reduce the risk of TB transmission at the human-animal interface.

### Table B3.5.1

<table>
<thead>
<tr>
<th>REGION</th>
<th>INCIDENCE</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>76,300 (20,300–168,000)</td>
<td>10,000 (25,700–22,500)</td>
</tr>
<tr>
<td>Americas</td>
<td>804 (218–1,770)</td>
<td>46 (12–98)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>7,490 (1,883–16,900)</td>
<td>639 (113–1,610)</td>
</tr>
<tr>
<td>Europe</td>
<td>12,900 (3,500–28,400)</td>
<td>103 (28–225)</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>47,400 (11,300–109,000)</td>
<td>2,280 (602–5,050)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>15,900 (4,290–34,900)</td>
<td>286 (77–630)</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td><strong>149,000 (71,600–255,000)</strong></td>
<td><strong>13,400 (5,050–25,700)</strong></td>
</tr>
</tbody>
</table>

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3.1.3 **Estimated trends in TB incidence, 2000–2015**

Consistent with previous global TB reports, the number of incident cases is falling slowly, in both absolute terms and per capita (Fig. 3.5, Fig. 3.6). Globally, the average rate of decline in the TB incidence rate was 1.4% per year in 2000–2015, and 1.5% between 2014 and 2015. This needs to accelerate to 4–5% per year by 2020 to achieve the milestones for reductions in cases and deaths set in the End TB Strategy (Chapter 2).

Trends are shown for the six WHO regions in Fig. 3.7 and for the 30 high TB burden countries in Fig. 3.8. The fastest declines are in the WHO European Region (3.3% per year from 2014 to 2015). The estimated decline in the incidence rate since 2010 has exceeded 4% per year in several high TB burden countries, including Zimbabwe (11%), Lesotho (7%), the United Republic of Tanzania (6.8%), Ethiopia (6.7%), Namibia (6.2%), Kenya (5.0%) and the Russian Federation (4.2%).

3.2 **TB mortality**

Deaths from TB among HIV-negative people are classified as TB deaths in the most recent version of the *International classification of diseases* (ICD-10).\(^1\) When an HIV-positive person dies from TB, the underlying cause is classified as HIV. For consistency with these classifications, this section makes a clear distinction between TB deaths in HIV-negative people and TB deaths in HIV-positive people.

3.2.1 **Methods to estimate TB mortality**

TB mortality among HIV-negative people can be measured directly using data from national vital registration (VR) systems, provided that these systems have high coverage and causes of death are accurately coded according to ICD-10. Sample VR systems covering representative areas

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of the country (e.g. as in China) provide an interim solution. Mortality surveys can also be used to estimate deaths caused by TB. In 2015, most countries with a high burden of TB lacked national or sample VR systems, and few had conducted mortality surveys. In the absence of VR systems or mortality surveys, TB mortality can be estimated as the product of TB incidence and the case fatality ratio (CFR), or from ecological modelling based on mortality data from countries with VR systems.

TB mortality among HIV-positive people is hard to measure even when VR systems are in place, because deaths among HIV-positive people are coded as HIV deaths and contributory causes (e.g. TB) are often not reliably recorded. TB deaths among HIV-positive people were estimated as the product of TB incidence and the CFR, with the latter accounting for the protective effect of antiretroviral therapy (ART).

Until 2008, WHO estimates of TB mortality used VR data for only three countries. This was substantially improved to 89 countries in 2009, although most of the data were from countries in the European Region and the Region of the Americas, which accounted for less than 10% of the world’s TB cases. For the current report, VR data were used for 128 countries (Fig. 3.9), which collectively accounted for 52% of the estimated number of TB deaths (among HIV-negative people) globally in 2015. The WHO African

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**FIG. 3.5**  
Global trends in the estimated number of incident TB cases and the number of TB deaths (in millions), 2000–2015. Shaded areas represent uncertainty intervals.

**FIG. 3.6**  
Global trends in estimated TB incidence and mortality rates, 2000–2015. The black line show notifications of new and relapse cases, for comparison with estimates of the total incidence rate. Shaded areas represent uncertainty intervals.
Region is the part of the world in which there is the greatest need to introduce or strengthen a VR system in which causes of death are classified according to ICD-10.

Details about the methods used to produce estimates of TB mortality are provided in the online technical appendix\(^1\) and in background documents prepared for the global review of methods used to produce TB burden estimates that was held in April 2015 (Box 3.1).

### 3.2.2 Estimates of TB mortality in 2015

Estimates of the number of deaths caused by TB are shown globally, for the six WHO regions and for the 30 high TB burden countries in Table 3.2. There were an estimated 1.4 million (range, 1.2 million to 1.6 million) deaths from TB among HIV-negative people in 2015 and an additional 0.39 million (range, 0.32 million to 0.46 million) deaths from TB among HIV-positive people. TB is one of the top 10 causes of death worldwide, and caused more deaths than HIV/AIDS in 2015 (Fig. 3.10, Fig. 3.11).\(^2\)

About 84% of TB deaths among HIV-negative people occurred in the WHO African Region and South-East Asia Region in 2015; these regions accounted for 86% of the combined total of TB deaths in HIV-negative and HIV-positive people. India and Nigeria accounted for 48% of global TB deaths among HIV-negative people and for 43% of the combined total TB deaths in HIV-negative and HIV-positive people.

Estimates of TB mortality rates (per 100 000 population) are shown globally, for the six WHO regions and for the 30 high TB burden countries in Table 3.3. Globally, the number of TB deaths among HIV-negative people per 100 000 population was 19 in 2015, and 24 when TB deaths among HIV-positive people were included. There was considerable variation among countries (Fig. 3.12), ranging from less than one TB death per 100 000 population in many high-income countries to more than 40 deaths per 100 000 population in much of the WHO African Region and in five high TB burden countries in Asia (Bangladesh, Cambodia, the Democratic People’s Republic of Korea, Myanmar and Papua New Guinea).

Estimates of the number of deaths caused by zoonotic TB are shown in Box 3.5.

### 3.2.3 Estimated trends in TB mortality, 2000–2015

Globally, the absolute number of TB deaths among HIV-negative people has been falling since 2000, from 1.8 million in 2000 to 1.4 million in 2015 (Fig. 3.5). The TB

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\(^1\) The online technical appendix is available at www.who.int/tb/data.

Trends in estimated TB incidence in the 30 high TB burden countries, 2000–2015. TB incidence rates are shown in green and incidence rates of HIV-positive TB are shown in red. Shaded areas represent uncertainty intervals. The black lines show notifications of new and relapse cases for comparison with estimates of the total incidence rate.

1 Estimates of TB incidence for Bangladesh will be reviewed once final results from the 2015/2016 national TB prevalence survey are available.

2 Estimates of TB incidence for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.
mortality rate (per 100,000 population) fell by 34% between 2000 and 2015 (Fig. 3.6), and by 2.7% between 2014 and 2015. Rates have also been falling in all six of the WHO regions (Fig. 3.13). Since 2010, the fastest average rates of decline in the mortality rate have been in the WHO Eastern Mediterranean and European regions (6.5% and 6.2% per year, respectively) and slowest in the WHO African Region (2.2% per year). Trends in mortality rates in the 30 high TB burden countries vary markedly (Fig. 3.14), ranging from substantial reductions since 2000 (e.g., China, Ethiopia, Myanmar, Pakistan the Philippines and the Russian Federation) to increases in Congo and the Democratic People’s Republic of Korea.

3.2.4 The case fatality ratio and across-country equity

The CFR is the proportion of people with TB who die from the disease; it can be approximated as the number of TB deaths divided by TB incidence in the same year. The CFR allows assessment of variation in equity in terms of access to TB diagnosis and treatment among countries because, if everyone with TB had access to timely diagnosis and high-quality treatment, the CFR would be low in all countries. To achieve the milestones for reductions in TB deaths set for 2020 and 2025 in the End TB Strategy, the global CFR needs to fall to 10% by 2020 and to 6% by 2025 (Chapter 2).

In 2015, the global CFR (calculated as the combined number of TB deaths in HIV-negative people and HIV-positive people divided by the total number of incident cases in both HIV-negative and HIV-positive people) was 17% and varied widely among countries (Fig. 3.15), from under 5% in a few countries to more than 20% in most countries in the WHO African Region. Intensified efforts are required to reduce the CFR to 10% globally by 2020.

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1 The CFR was calculated based on the combined total of deaths in HIV-negative and HIV-positive people for the purpose of cross-country comparisons, in particular to illustrate the high CFRs in African countries that could be reduced by effective detection and care programmes. CFRs restricted to HIV-negative TB deaths and cases can also be calculated but are not shown. At the subnational level, CFRs can also be restricted to HIV-negative TB deaths, depending on the country and its HIV burden.
**FIG. 3.10a**

Top causes of death worldwide in 2012.\(^{a,b,c,d}\) Deaths from TB among HIV-positive people are shown in grey.\(^d\)

![Bar chart showing top causes of death worldwide in 2012](chart)

\(^a\) Estimates of causes of death will be updated by WHO before the end of 2016.

\(^b\) This is the latest year for which estimates for all causes are currently available. See WHO Global Health Observatory data repository, available at http://apps.who.int/gho/data/node.main.GHECOD (accessed 28 July 2016).

\(^c\) For HIV/AIDS, the latest estimates of the number of deaths in 2012 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2016/HIV_estimates_with_uncertainty_bounds_1990-2015. For TB, the estimates for 2012 are those published in this report.

\(^d\) Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

**FIG. 3.10b**

Estimated number of deaths from HIV/AIDS and TB in 2015. Deaths from TB among HIV-positive people are shown in grey.\(^{a,b}\)

![Bar chart showing estimated number of deaths from HIV/AIDS and TB in 2015](chart)

\(^a\) For HIV/AIDS, the latest estimates of the number of deaths in 2015 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2016/HIV_estimates_with_uncertainty_bounds_1990-2015. For TB, the estimates for 2015 are those published in this report.

\(^b\) Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

**FIG. 3.11**

Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000–2015.\(^{a,b}\)

Shaded areas represent uncertainty intervals.

![Graph showing global trends in the estimated number of deaths caused by TB and HIV (in millions), 2000–2015](graph)

\(^a\) For HIV/AIDS, the latest estimates of the number of deaths in 2015 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2016/HIV_estimates_with_uncertainty_bounds_1990-2015. For TB, the estimates for 2015 are those published in this report.

\(^b\) Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

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### 3.2.5 Estimated number of deaths averted by TB treatment, 2000–2015

The actual numbers of TB deaths (presented above) can be compared with the number of TB deaths that would have occurred in the absence of TB treatment to give an estimate of the deaths averted by TB interventions. The number of deaths that would have occurred each year in the absence of TB treatment (and without ART provided alongside TB treatment for HIV-positive cases) can be conservatively estimated as the number of estimated incident cases (Section 3.1) multiplied by the relevant estimated CFR for untreated TB.\(^1\) Estimates are conservative because they do not account for the impact of TB control or ART on the level of TB incidence, or for the indirect, downstream impact of these interventions on future levels of infections, cases and deaths.

Between 2000 and 2015, TB treatment alone averted an estimated 39 million deaths among HIV-negative people (Table 3.4). Among HIV-positive people, TB treatment supported by ART averted an additional 9.6 million deaths.

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\(^1\) Further details about methods used to estimate lives saved, including CFRs for different categories of TB case, are provided in the online technical appendix, available at www.who.int/tb/data.
### FIG. 3.12

**Estimated TB mortality rates in HIV-negative people, 2015**

<table>
<thead>
<tr>
<th>Rate per 100,000 population</th>
<th>0–0.9</th>
<th>1–4.9</th>
<th>5–19.9</th>
<th>20–39</th>
<th>≥40</th>
<th>No data</th>
<th>Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0–14</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>15–24</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>25–34</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>35–44</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>45–64</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>65+</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### FIG. 3.13

**Regional trends in estimated TB mortality rates (log scale), 2000–2015.** TB mortality rates in HIV-negative people are shown in blue and mortality rates of HIV-positive TB are shown in red. Shaded areas represent uncertainty intervals.
FIG. 3.14
Trends in estimated TB mortality rates, 2000–2015, in the 30 high TB burden countries. TB mortality rates in HIV-negative people are shown in blue and mortality rates of HIV-positive TB are shown in red. The black lines show observations from vital registration systems. Shaded areas represent uncertainty intervals.\textsuperscript{a,b}

\textsuperscript{a} Estimates of TB mortality for Bangladesh will be reviewed once final results from the 2015/2016 national TB prevalence survey are available.

\textsuperscript{b} Estimates of TB mortality for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.
3.3 Drug-resistant TB

3.3.1 Global surveillance of anti-TB drug resistance

Since the launch of the Global Project on Anti-tuberculosis Drug Resistance Surveillance in 1994, data on drug resistance have been systematically collected and analysed from 155 countries worldwide (80% of 194 WHO Member States), which collectively have more than 95% of the world’s population and TB cases. This includes 83 countries that have continuous surveillance systems based on routine diagnostic drug-susceptibility testing (DST) of Mycobacterium tuberculosis isolates obtained from all TB patients, and 72 countries that rely on epidemiological surveys of bacterial isolates collected from representative samples of patients (Fig. 3.16). Surveys conducted every 5 years represent the most common approach to investigating the burden of drug resistance in resource-limited settings where routine DST is not accessible to all TB patients owing to lack of laboratory capacity or resources.

Progress towards achieving global coverage of drug resistance surveillance data is shown in Fig. 3.17. Among the 30 high TB burden countries and 30 high MDR-TB burden countries (which comprise a total of 40 countries, given

:: TABLE 3.4
Cumulative number of deaths averted by TB and TB/HIV interventions 2000–2015 (in millions), globally and by WHO region

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>HIV-NEGATIVE PEOPLE</th>
<th>HIV-POSITIVE PEOPLE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
</tr>
<tr>
<td>Africa</td>
<td>4.6</td>
<td>3.6–5.5</td>
<td>6.6</td>
</tr>
<tr>
<td>The Americas</td>
<td>1.4</td>
<td>1.2–1.5</td>
<td>0.32</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>2.8</td>
<td>2.3–3.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Europe</td>
<td>2.2</td>
<td>1.9–2.4</td>
<td>0.17</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>19</td>
<td>15–22</td>
<td>1.9</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>9.8</td>
<td>8.8–11</td>
<td>0.32</td>
</tr>
<tr>
<td>Global</td>
<td>39</td>
<td>34–45</td>
<td>9.6</td>
</tr>
</tbody>
</table>

:: FIG. 3.15
Estimates of the case fatality ratio (CFR), (including HIV-negative and HIV-positive people), 2015
Data sources available to estimate levels of TB drug resistance

Global coverage of surveillance data on drug resistance, 1995–2016
overlap between the two groups). 37 have data on levels of drug resistance. The three countries that have never conducted a drug resistance survey are Angola, Congo and Liberia. Among the other 37 high TB burden countries, the data for Sierra Leone are from before the year 2000, and five countries (Brazil, Central African Republic, Democratic People’s Republic of Korea, Papua New Guinea and the Russian Federation) rely on drug-resistance surveillance data gathered from subnational areas only.

In 2015, the first-ever drug resistance survey was completed in Djibouti, and repeat surveys were completed in Kenya, Lesotho, Namibia, Romania, Rwanda and South Africa. In 2016, drug resistance surveys were ongoing in 11 countries, with the first nationwide surveys in seven countries (Burkina Faso, the Democratic Republic of the Congo, Ghana, India, Indonesia, Lao People’s Democratic Republic and Sudan) and repeat surveys in four countries (China, Côte d’Ivoire, Swaziland and Zimbabwe).

3.3.2 Estimates of the disease burden caused by MDR/RR-TB

In previous global TB reports, estimates of the burden of drug-resistant TB have focused on MDR-TB (defined as resistance to rifampicin and isoniazid, the two most effective anti-TB drugs). In May 2016, WHO issued guidance that people with TB resistant to rifampicin, with or without resistance to other drugs, should be treated with an MDR-TB treatment regimen. This includes patients with MDR-TB as well as any other patient with TB resistant to rifampicin (referred to in this report as MDR/RR-TB). Following that guidance, estimates of the burden of MDR/RR-TB are required for assessing progress in detection of cases with drug-resistant TB and treatment coverage.

Globally in 2015, an estimated 3.9% (95% confidence interval [CI]: 2.7–5.1%) of new cases and 21% (95% CI: 15–28%) of previously treated cases had MDR/RR-TB (Table 3.5). The proportions of new and previously treated TB cases with MDR/RR-TB at the country level are shown in Fig. 3.18 and Fig. 3.19.

There were an estimated 580 000 (range, 520 000–640 000) incident cases of MDR/RR-TB in 2015, with cases of MDR-TB accounting for 83% of the total (Table 3.5). The number of MDR-TB incident cases (480 000) is in line with the estimate published in 2015. The countries with the largest numbers of MDR/RR-TB cases (45% of the global total) are China, India and the Russian Federation (Fig. 3.20).

There were about 250 000 (range, 160 000–340 000) deaths from MDR/RR-TB in 2015. The best estimate is slightly higher than estimates of deaths from MDR-TB published in recent global TB reports, due to the inclusion of deaths from all cases with RR-TB (and not only those with MDR-TB).

Data compiled from surveys and continuous surveillance of drug resistance among TB patients also allow estimation of the number of MDR/RR-TB cases among notified TB patients with pulmonary TB. These are the MDR/RR-TB cases that could be detected if all notified patients were tested for drug resistance to rifampicin and isoniazid using WHO-recommended diagnostic tests. Globally in 2015, there were an estimated 340 000 (range, 320 000–350 000) MDR/RR-TB cases among notified TB patients. Country-specific estimates are presented and discussed in Chapter 4.

3.3.3 Trends in drug resistance

Of the 40 countries with a high TB or MDR-TB burden (or both), only 20 have repeated a survey at least once to evaluate trends in drug resistance. Among these countries, eight have at least 3 years of data: Belarus, Kazakhstan, Myanmar, Peru, Republic of Moldova, Tomsk Oblast in the Russian Federation, Thailand and Viet Nam. For these settings, trends in the number of new TB cases notified, the proportion of new TB cases with MDR, and per capita TB and MDR-TB rates are shown in Fig. 3.21. Based on these data, there is a slight trend for cases of MDR-TB to increase as a proportion of all TB cases in these countries, with the burden of MDR-TB either increasing faster or decreasing more slowly than the overall TB burden in each country.

3.3.4 Resistance to second-line anti-TB drugs and pyrazinamide

By the end of 2015, extensively drug-resistant TB (XDR-TB) had been reported by 117 WHO Member States. Of these, 88 countries and five territories reported representative data from continuous surveillance or surveys regarding the proportion of MDR-TB cases that had XDR-TB. Combining their data, the average proportion of MDR-TB cases with XDR-TB was 9.5% (95% CI: 7.0–12.1%), similar to estimates for previous years (9.7% in 2014 and 9.0% in 2013).

Among the 40 countries with a high TB or MDR-TB burden, 21 have surveillance data on resistance to second-line anti-TB drugs, but only six have established a national continuous surveillance system for second-line drug resistance among patients with MDR-TB. The proportion of MDR-TB cases with resistance to any fluoroquinolone for which testing was done – including ofloxacin, levofloxacin and moxifloxacin – was 21.0% (95% CI: 8.8–33.3%). A total of 51% (30–70%) of patients with MDR-TB have resistance to a fluoroquinolone or a second-line injectable agent, or both. Levels of resistance to fluoroquinolones and pyrazinamide among all TB cases have been studied in a multicountry surveillance project; results are summarized in Box 3.6.
## TABLE 3.5
Estimated incidence of MDR/RR-TB in 2015 for 30 high MDR-TB burden countries, WHO regions and globally

<table>
<thead>
<tr>
<th></th>
<th>ESTIMATED % OF NEW CASES WITH MDR/RR-TB</th>
<th>ESTIMATED % OF PREVIOUSLY TREATED CASES WITH MDR/RR-TB</th>
<th>INCIDENCE OF MDR/RR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEST ESTIMATE</td>
<td>UNCERTAINTY INTERVAL</td>
<td>BEST ESTIMATE</td>
</tr>
<tr>
<td>Angola</td>
<td>2.8</td>
<td>0.1-6.7</td>
<td>21</td>
</tr>
<tr>
<td>Azerbaijan</td>
<td>13</td>
<td>10-16</td>
<td>29</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>1.6</td>
<td>0.59-2.6</td>
<td>29</td>
</tr>
<tr>
<td>Belarus</td>
<td>37</td>
<td>35-39</td>
<td>69</td>
</tr>
<tr>
<td>China</td>
<td>6.6</td>
<td>5.3-7.9</td>
<td>30</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>2.2</td>
<td>0.51-3.9</td>
<td>16</td>
</tr>
<tr>
<td>DR Congo</td>
<td>3.2</td>
<td>1.4-5.0</td>
<td>14</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>2.7</td>
<td>1.5-4.0</td>
<td>14</td>
</tr>
<tr>
<td>India</td>
<td>2.5</td>
<td>2.1-3.1</td>
<td>16</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.8</td>
<td>2.2-3.5</td>
<td>16</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>25</td>
<td>24-26</td>
<td>43</td>
</tr>
<tr>
<td>Kenya</td>
<td>1.3</td>
<td>0.68-1.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Kyrgyzstan</td>
<td>32</td>
<td>28-36</td>
<td>56</td>
</tr>
<tr>
<td>Mozambique</td>
<td>3.7</td>
<td>2.4-5.0</td>
<td>20</td>
</tr>
<tr>
<td>Myanmar</td>
<td>5.1</td>
<td>3.2-7.0</td>
<td>27</td>
</tr>
<tr>
<td>Nigeria</td>
<td>4.3</td>
<td>3.2-5.4</td>
<td>25</td>
</tr>
<tr>
<td>Pakistan</td>
<td>4.2</td>
<td>3.2-5.3</td>
<td>16</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>3.4</td>
<td>1.7-5.0</td>
<td>26</td>
</tr>
<tr>
<td>Peru</td>
<td>5.9</td>
<td>5.6-6.3</td>
<td>21</td>
</tr>
<tr>
<td>Philippines</td>
<td>2.6</td>
<td>1.8-3.3</td>
<td>29</td>
</tr>
<tr>
<td>Republic of Moldova</td>
<td>32</td>
<td>29-34</td>
<td>69</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>22</td>
<td>14-25</td>
<td>53</td>
</tr>
<tr>
<td>Somalia</td>
<td>8.7</td>
<td>5.9-11</td>
<td>47</td>
</tr>
<tr>
<td>South Africa</td>
<td>3.5</td>
<td>2.8-4.2</td>
<td>71</td>
</tr>
<tr>
<td>Tajikistan</td>
<td>14</td>
<td>12-15</td>
<td>77</td>
</tr>
<tr>
<td>Thailand</td>
<td>2.2</td>
<td>1.5-2.9</td>
<td>24</td>
</tr>
<tr>
<td>Ukraine</td>
<td>25</td>
<td>21-28</td>
<td>58</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>24</td>
<td>18-30</td>
<td>63</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>4.1</td>
<td>2.6-5.5</td>
<td>25</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>3.2</td>
<td>1.4-5.0</td>
<td>14</td>
</tr>
<tr>
<td>High MDR/RR-TB burden countries</td>
<td>4.3</td>
<td>2.7-5.8</td>
<td>22</td>
</tr>
<tr>
<td>Africa</td>
<td>3.0</td>
<td>1.2-4.9</td>
<td>15</td>
</tr>
<tr>
<td>The Americas</td>
<td>2.9</td>
<td>1.6-4.2</td>
<td>12</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>4.1</td>
<td>3.0-5.1</td>
<td>17</td>
</tr>
<tr>
<td>Europe</td>
<td>16</td>
<td>11-20</td>
<td>48</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>2.6</td>
<td>2.3-3.0</td>
<td>17</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>5.1</td>
<td>3.0-7.2</td>
<td>26</td>
</tr>
<tr>
<td>Global</td>
<td>3.9</td>
<td>2.7-5.1</td>
<td>21</td>
</tr>
</tbody>
</table>

a Best estimates are for the latest available year.
b Rates are per 100,000 population.
Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2001 are not shown.

Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2001 are not shown. The high percentages of previously treated TB cases with MDR-TB in Bahamas, Bahrain, Belize, Bonaire – Saint Eustatius and Saba, French Polynesia and Sao Tome and Principe refer to only a small number of notified cases (range: 1-8 notified previously treated TB cases).
:: FIG. 3.20
Estimated incidence of MDR/RR-TB in 2015, for countries with at least 1000 incident cases. Areas that are not applicable are in grey.

:: Box 3.6
Resistance to pyrazinamide and fluoroquinolones: a summary of results from the first surveys in five countries

The combination of pyrazinamide plus a fourth-generation fluoroquinolone (moxifloxacin or gatifloxacin) is considered essential in novel rifampicin-sparing regimens for the treatment of TB and in shorter regimens for the treatment of MDR-TB. Understanding the background prevalence at population level of resistance to these drugs is important to assess the feasibility of introducing new and shorter regimens in TB control programmes.

Although levels of resistance to rifampicin and isoniazid are monitored in most TB-endemic countries through drug-resistance surveys, testing for susceptibility to fluoroquinolones and pyrazinamide is not routinely performed as part of surveillance efforts. Therefore, population-representative surveillance data on levels of resistance to these drugs are limited. To start to address this knowledge gap, a multicountry project was coordinated by WHO in five countries – Azerbaijan, Bangladesh, Belarus, Pakistan and South Africa – enrolling more than 5000 patients. Results from this project were published in May 2016a and a summary is provided here.

Levels of resistance varied substantially among settings (3.1–42.1%). In all settings, pyrazinamide resistance was significantly associated with rifampicin resistance (0.5–4.2% among rifampicin-resistant cases). Resistance ranged from 1.0% to 16.6% for ofloxacin, from 0.5% to 12.4% for levofloxacin and from 0.9% to 14.6% for moxifloxacin when tested at 0.5 µg/ml. High levels of ofloxacin resistance were found in Pakistan. Resistance to moxifloxacin and gatifloxacin when tested at 2 µg/ml was low in all countries. Cross-resistance was high between ofloxacin and levofloxacin (87%) and between ofloxacin and moxifloxacin (72%) when tested at 0.5 µg/ml. Cross-resistance was very low between ofloxacin and moxifloxacin when tested at 2 µg/ml.

The presence of rifampicin resistance, which currently is easily identified because of the wide availability of new rapid molecular technology, should prompt attention to the possibility of the simultaneous presence of resistance to pyrazinamide and, in some settings, the earlier generation fluoroquinolones. Resistance to the latest generation fluoroquinolones at the clinical breakpoint is still uncommon, a finding that supports current WHO recommendations to use moxifloxacin or gatifloxacin in the treatment of MDR-TB.

3.4 National TB prevalence surveys

The prevalence of TB disease is not an indicator in the SDGs or a high-level indicator of the End TB Strategy, and no global target has been set for the period post-2015. This is in contrast to the era of the Millennium Development Goals (MDGs) and Stop TB Strategy, when one of the global targets for reductions in TB disease burden was to halve prevalence between 1990 and 2015. Furthermore, indirect estimates of prevalence suffer from considerable uncertainty, because they are derived from incidence and assumptions about disease duration. Hence, indirect estimates of TB prevalence are not presented in this chapter.¹

These developments notwithstanding, in an important subset of countries with a large proportion of the world’s TB burden, national TB prevalence surveys will continue to provide the best method for measuring the burden of TB disease (both in absolute terms and to assess trends when repeat surveys are done), and related assessment of actions needed to reduce that burden. This group of countries can be broadly defined as those with a relatively high burden of TB (about 150 incident cases per 100,000 population)² that do not yet have health, national notification and VR systems of the quality and coverage required to provide reliable and routine direct measurements of the number of TB cases and deaths. In addition, results from national TB prevalence surveys can inform estimates of TB incidence and mortality, and thus contribute to monitoring

¹ WHO will continue to produce indirect estimates of TB prevalence. These can be provided upon request to tbdata@who.int.

² In low- and medium-burden countries, sample sizes and costs for surveys become prohibitively large.
of progress towards SDG and End TB Strategy targets. For these reasons, the status of progress in implementation of national TB prevalence surveys, and summaries of key results, will continue to be featured in global TB reports.

There has already been substantial progress in the number of countries that have implemented a national TB prevalence survey. This was particularly the case during the period 2007–2015, when the WHO Global Task Force on TB Impact Measurement defined national TB prevalence surveys in 22 global focus countries as one of its three strategic areas of work for the period up to the end of 2015. In Africa, these countries included Ethiopia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Uganda, UR Tanzania and Zambia. In Asia, these countries included Bangladesh, Cambodia, China, Indonesia, Myanmar, Pakistan, Philippines, Thailand and Viet Nam.

1 In 2007, the WHO Global Task Force on TB Impact Measurement defined national TB prevalence surveys in 22 global focus countries as one of its three strategic areas of work for the period up to the end of 2015. In Africa, these countries included Ethiopia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Uganda, UR Tanzania and Zambia. In Asia, these countries included Bangladesh, Cambodia, China, Indonesia, Myanmar, Pakistan, Philippines, Thailand and Viet Nam.


3 Examples of how survey data can provide important insights into the distribution of TB disease by age, sex and location, as well as differences in detection and reporting of cases by age and sex, are provided in Section 3.6.1.
Countries in which national population-based surveys of the prevalence of TB disease have been implemented using currently recommended screening and diagnostic methods* since 2000 or are planned in the future (status in August 2016)

Estimates of TB prevalence (all ages, all forms of TB) for 19 countries, before (in blue) and after (in red) survey results from national TB prevalence surveys became available. Panels are ordered according to the before-after difference.
Number of TB cases found in national TB prevalence surveys implemented 2009-2015, and associated estimates of the prevalence of pulmonary TB in adults (aged ≥15 years)

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>MAIN YEAR(S) OF SURVEY</th>
<th>NUMBER OF SMEAR-POSITIVE CASES</th>
<th>NUMBER OF BACTERIOLOGICALLY CONFIRMED CASES</th>
<th>PREVALENCE PER 100 000 POPULATION: SMEAR-POSITIVE CASES</th>
<th>PREVALENCE PER 100 000: BACTERIOLOGICALLY CONFIRMED CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BEST ESTIMATE 95% CONFIDENCE INTERVAL</td>
<td>BEST ESTIMATE 95% CONFIDENCE INTERVAL</td>
</tr>
<tr>
<td>Cambodia</td>
<td>2011</td>
<td>103</td>
<td>314</td>
<td>271</td>
<td>212–348</td>
</tr>
<tr>
<td>China</td>
<td>2010</td>
<td>188</td>
<td>347</td>
<td>66</td>
<td>53–79</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>2010-2011</td>
<td>47</td>
<td>110</td>
<td>108</td>
<td>73–143</td>
</tr>
<tr>
<td>Gambia</td>
<td>2012</td>
<td>34</td>
<td>77</td>
<td>90</td>
<td>53–127</td>
</tr>
<tr>
<td>Ghana</td>
<td>2013</td>
<td>64</td>
<td>202</td>
<td>111</td>
<td>76–145</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2013-2014</td>
<td>165</td>
<td>426</td>
<td>257</td>
<td>210–303</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>2010-2011</td>
<td>107</td>
<td>237</td>
<td>278</td>
<td>199–356</td>
</tr>
<tr>
<td>Malawi</td>
<td>2013</td>
<td>62</td>
<td>132</td>
<td>220</td>
<td>142–297</td>
</tr>
<tr>
<td>Myanmar</td>
<td>2009-2010</td>
<td>123</td>
<td>311</td>
<td>242</td>
<td>186–315</td>
</tr>
<tr>
<td>Nigeria</td>
<td>2012</td>
<td>107</td>
<td>144</td>
<td>318</td>
<td>225–412</td>
</tr>
<tr>
<td>Pakistan</td>
<td>2010-2011</td>
<td>233</td>
<td>341</td>
<td>270</td>
<td>217–322</td>
</tr>
<tr>
<td>Rwanda</td>
<td>2012</td>
<td>27</td>
<td>40</td>
<td>74</td>
<td>48–99</td>
</tr>
<tr>
<td>Sudan</td>
<td>2013-2014</td>
<td>57</td>
<td>112</td>
<td>87</td>
<td>54–118</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>2012</td>
<td>134</td>
<td>—</td>
<td>275</td>
<td>232–326</td>
</tr>
<tr>
<td>Thailand</td>
<td>2012</td>
<td>58</td>
<td>142</td>
<td>104</td>
<td>55–195</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>2014</td>
<td>23</td>
<td>107</td>
<td>82</td>
<td>53–128</td>
</tr>
</tbody>
</table>

a Estimates based upon the use of robust standard errors with missing value imputation and inverse probability weighting for all countries except for Cambodia, Myanmar and UR Tanzania which used a cluster-level model of analysis without imputation.

b Laboratory challenges meant that it was only possible to directly estimate the prevalence of smear-positive (as oppose to bacteriologically confirmed) TB.

c Data excludes clusters from the capital city, Bangkok.

Estimates of TB incidence (all ages, all forms of TB) for 13 countries that implemented a national TB prevalence survey in the period 2012-2015, before (in blue) and after (in red) survey results became available
3.5 Estimates of TB incidence and mortality disaggregated by age and sex

This section presents estimates of TB incidence and TB mortality disaggregated by age and sex.

3.5.1 Methods to disaggregate estimates by age and sex

Estimates of TB incidence disaggregated by age and sex were produced by assuming that the male to female (M:F) ratio of notified cases (with adults and children considered separately) was the same as the ratio for incident cases. This assumption is reasonable for children (defined as people aged under 15 years), but is recognized to be problematic for some countries, given evidence from recent prevalence surveys that case detection and reporting gaps are often larger for adult men compared with adult women (Section 3.6.1). Resulting estimates may thus understage the burden of TB in men compared with women.

For 113 countries, (all of which were middle- or high-income countries in 2015), estimates of TB deaths among HIV-negative adults were produced using age and sex-disaggregated mortality data from VR systems. For countries without VR data, estimates were produced using an imputation model that included risk factors known to be associated with TB mortality. TB deaths among HIV-positive people were disaggregated by age and sex using the assumption that the M:F and children:adult ratios are similar to the corresponding ratios of AIDS deaths estimated by the Joint United Nations Programme on HIV/AIDS (UNAIDS).

Details of the methods used are provided in the online technical appendix.²

3.5.2 TB incidence disaggregated by age and sex

Estimates of TB incidence are shown for males and females, both in total and by age group (adults and children), in Fig. 3.26. Globally in 2015, there were an estimated 6.4 million (range, 5.7 million to 7.2 million) incident cases of TB among males, of which 5.9 million (range, 5.3 million to 6.7 million) were adults and 0.47 million (range, 0.42 million to 0.53 million) were children. There were 4.0 million (range, 3.1 million to 4.9 million) incident cases of TB in females, of which 3.5 million (range, 2.7 million to 4.4 million) were adults and 0.48 million (range, 0.41 million to 0.56 million) were children. These numbers correspond to 62% of cases being males and 38% females, and 90% of cases being adults and 10% children. Further breakdowns by HIV status are not possible, because data on the HIV status of TB cases by age and sex are not available.

The M:F ratio of incident TB cases for all ages ranged from 1.1 in the WHO Eastern Mediterranean Region to 2.0 in the Western Pacific Region. Similar M:F ratios were estimated for adults, whereas for children the M:F ratio ranged from 0.9 in the WHO Eastern Mediterranean Region to 1.1 in the Western Pacific Region. Most of the estimated cases among males in 2015 were in Asia (63%) and the WHO African Region (25%), whereas for females the percentages were 58% for Asia and 28% for the WHO African Region, respectively. For children, the top three regions were the WHO South-East Asia Region with 40% of incident TB cases in 2015, followed by the African Region with 31% and the Western Pacific Region with 14%.

1 Adults are defined as those aged ≥15 years because this is consistent with the age categories for which notification data are reported, and with the cut-off used in current guidelines to define people eligible to participate in a TB prevalence survey.

2 The online technical appendix is available at www.who.int/tb/data.

3 Asia refers to the WHO Regions of South-East Asia and the Western Pacific.
The age distribution of adult TB cases detected in prevalence surveys implemented 2009–2015

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>TOTAL 0-14 YEARS</th>
<th>0-14 YEARS</th>
<th>MALE ≥15 YEARS</th>
<th>FEMALE ≥15 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>448 000</td>
<td>63 500</td>
<td>274 000</td>
<td>110 000</td>
</tr>
<tr>
<td>The Americas</td>
<td>18 500</td>
<td>2 170</td>
<td>11 700</td>
<td>4 670</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>79 800</td>
<td>10 500</td>
<td>49 400</td>
<td>19 900</td>
</tr>
<tr>
<td>Europe</td>
<td>32 100</td>
<td>521</td>
<td>18 700</td>
<td>12 900</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>712 000</td>
<td>83 900</td>
<td>447 000</td>
<td>181 000</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>89 500</td>
<td>8 300</td>
<td>57 600</td>
<td>23 600</td>
</tr>
<tr>
<td>Global</td>
<td>1 380 000</td>
<td>169 000</td>
<td>858 000</td>
<td>353 000</td>
</tr>
</tbody>
</table>

HIV-POSITIVE

<table>
<thead>
<tr>
<th>WHO REGION</th>
<th>TOTAL 0-14 YEARS</th>
<th>0-14 YEARS</th>
<th>MALE ≥15 YEARS</th>
<th>FEMALE ≥15 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>295 000</td>
<td>34 000</td>
<td>142 000</td>
<td>120 000</td>
</tr>
<tr>
<td>The Americas</td>
<td>5 890</td>
<td>200</td>
<td>3 870</td>
<td>1 820</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>2 970</td>
<td>310</td>
<td>1 760</td>
<td>847</td>
</tr>
<tr>
<td>Europe</td>
<td>4 870</td>
<td>47</td>
<td>3 490</td>
<td>1 330</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>74 300</td>
<td>610</td>
<td>49 500</td>
<td>18 600</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>5 750</td>
<td>270</td>
<td>4250</td>
<td>1 230</td>
</tr>
<tr>
<td>Global</td>
<td>389 000</td>
<td>41 000</td>
<td>204 000</td>
<td>143 000</td>
</tr>
</tbody>
</table>

The age distribution of adult TB cases detected in prevalence surveys implemented 2009–2015

Asia

Africa

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3.5.3 TB mortality disaggregated by age and sex

Estimates of TB mortality disaggregated by age and sex are shown in Table 3.7. Estimates are shown for HIV-positive and HIV-negative people separately, given that the cause of TB deaths among HIV-positive people is classified as HIV in ICD-10 (see also Section 3.2).

TB mortality among HIV-negative people

Globally in 2015, there were an estimated 0.86 million (range, 0.77 million to 0.95 million) deaths from TB among HIV-negative men. There were an additional 0.35 million (range, 0.27 million to 0.45 million) deaths from TB among HIV-negative women, and 0.17 million (range, 0.15 to 0.19 million) among children. These numbers correspond to 62% of deaths being in men, 25% in women, and 13% in children. Higher numbers of TB deaths among men are consistent with the estimate that 62% of incident cases were among men in 2015, and with evidence from prevalence surveys that show that TB disease affects men more than women (Fig. 3.28) and that case detection and reporting gaps are higher among men (Fig. 3.29). The WHO South-East Asia and African regions accounted for more than 80% of TB deaths among HIV-negative people.

TB mortality among HIV-positive people

There were an estimated 0.20 million (range, 0.18 million to 0.23 million) TB deaths among HIV-positive men, 0.14 million (range, 0.12 million to 0.17 million) among HIV-positive women and 0.04 million (range, 0.03 million to 0.05 million) among HIV-positive children in 2015 (Table 3.7). The WHO African Region accounted for 75% of these deaths, where the M:F ratio was close to one. The M:F ratio in other regions varied from about 2 to 4.

3.6 Disaggregated analysis of TB surveillance and survey data

Disaggregated analysis of national TB surveillance and survey data is important to understand how the TB epidemic varies geographically and which population groups are most affected. The results can be used to inform national and local response efforts, including strategic allocation of resources. The importance of such within-country analyses and disaggregation of key indicators is emphasized within the End TB Strategy and the SDGs (Chapter 2). This section showcases examples of such analyses.

3.6.1 TB prevalence survey data disaggregated by age, sex and location

Results from national TB prevalence surveys (Section 3.4) provide representative data about the distribution of TB disease by age (in adults) and sex. The prevalence of disease per 100 000 population for three age groups found in surveys implemented in 2009–2015 is shown in Fig. 3.27. In Asia and some African countries (e.g. Ghana, Malawi, Rwanda, the United Republic of Tanzania and Zimbabwe), prevalence increases with age. In several African countries (e.g. Ethiopia, Gambia, Sudan, Uganda and Zambia), however, prevalence per 100 000 population peaks among those aged 35–54 years. The M:F ratio of cases for the same set of surveys is shown in Fig. 3.28. These show a systematically higher burden of TB disease among men, with ratios ranging from 1.5 (in Ethiopia) to 6.0 (in Rwanda).
for smear-positive TB, and from 1.2 (in Ethiopia) to 4.5 (in Viet Nam) for bacteriologically confirmed TB.

The ratio of prevalence to notification (P:N) can be used to assess detection and reporting gaps (Fig. 3.29a), and variation in these gaps by age and sex (Fig. 3.29b). The P:N ratios from surveys implemented in 2009–2015 indicate that women are probably accessing available diagnostic and treatment services more effectively than men. The higher disease burden in men, combined with larger detection and reporting gaps, also suggests that strategies to improve access to and use of health services among men are required.

Due to sample-size requirements, feasibility and budget restrictions, most of the national TB prevalence surveys carried out since 2000 produced a single national estimate of high statistical precision. However, there can still be value in subnational estimates, especially for hypothesis building, and to identify potential priority areas for further evidence generation and subsequent action. In Nigeria, the national TB programme (NTP) identified states that had high levels of TB prevalence but large gaps in surveillance systems in terms of the actual number of cases being detected, treated and notified (Fig. 3.30).

3.6.2 The case fatality ratio disaggregated by age, sex and location – an example from Brazil

As explained in Section 3.2.4, the CFR is the proportion of people with TB who die from the disease, and it is an important indicator for monitoring progress towards SDG and End TB Strategy milestones set for 2020 and 2025.
Reaching the milestones for reductions in the number of TB deaths requires the CFR at global level to fall to 10% by 2020 and to 6.5% by 2025. The CFR is one of the top priority indicators for monitoring implementation of the End TB Strategy (Chapter 2).

In countries with national notification and VR systems of sufficient quality and coverage, the number of TB deaths measured using national VR data divided by the number of notified new and relapse cases in the same time period provides a good approximation of the CFR. Since notification and VR data are available for subnational areas and are disaggregated by age and sex, the CFR can then be estimated for subnational areas and subpopulations (in addition to the global and national estimates discussed in Section 3.2.4). This is useful because it can help to identify within-country inequalities and inequities in access to TB diagnosis and treatment. If everyone had similar and good access to diagnosis and treatment, for example, the CFR should be low for all areas and subpopulations.

Brazil is an example of a high TB burden country that has both a VR system (called SIM) of national coverage\(^1\) and a notifiable disease surveillance system (called SINAN) that is thought to capture most incident cases of TB (the best estimate is 87%, as shown in the country profile for Brazil in Annex 2). It thus provides a good example of how CFRs can be assessed at subnational level and for subpopulations.

The distribution of the CFR in Brazil by state in the years 2011–2014 is shown in Fig. 3.31a–b. There was a two-fold difference in the average CFR between the state with the highest average CFR (Alagoas, 11.3%) and the state with the lowest average CFR (Acre, 5.7%). The distribution of the CFR by sex in 2014 is shown in Fig. 3.31c. The CFR was higher among males than females, although there was considerable overlap between the two distributions.\(^2\) The relationship between the CFR and age in 2014 is shown in Fig. 3.31d. This shows a positive relationship between age and the CFR, with marked differences between those aged 15–59 years and those aged over 60 years.

The variation in the CFR estimated in Brazil probably reflects a combination of differences in case detection, the quality of care and the coverage of reporting. These can be further explored through record-linkage studies using the violin plots shown in Fig. 3.31c–d are similar to box plots, but they also show the probability density of the data at different values.

\(^1\) http://www.who.int/healthinfo/statistics/mortcoverage/en/  
\(^2\) The violin plots shown in Fig. 3.31c–d are similar to box plots, but they also show the probability density of the data at different values.
The distribution of state CFRs by sex in Brazil, 2014.

Horizontal segments denote the average.

These violin plots are used to visualise the distribution of the data and its probability density. It is a combination of a box plot and a density plot that is rotated and placed on each side, to show the distributional shape of the data.

The distribution of state CFRs by age in Brazil, 2014.

Horizontal segments denote the average.

These violin plots are used to visualise the distribution of the data and its probability density. It is a combination of a box plot and a density plot that is rotated and placed on each side, to show the distributional shape of the data.
:: Box 3.7
Promoting the analysis and use of disaggregated data for policy, planning and programmatic action

:: FIG. B 3.7.1
Subnational TB notifications (new and relapse, 2015) from Ghana, Guinea, Nigeria and Sierra Leone

Strong TB surveillance systems allow the TB epidemic to be tracked at national level, and for subnational areas and specific population groups, using routinely collected data. The results can be used to inform national and local response efforts, including strategic allocation of resources.

As part of efforts to improve the availability and facilitate the analysis of disaggregated TB surveillance data by age, sex and location, a pilot workshop was held in May 2016 with the NTPs of 16 countries in west Africa. In TB epidemiological reviews (Fig. 3.1b), a common finding was that historical subnational data were stored in multiple separate spreadsheets that made it difficult to use the available data. In response to this finding, preparations for the workshop included the development of a standard platform for safeguarding and analysing subnational notification and treatment outcome data. This platform was developed using the DHIS2 software, which is open source and is already used for collecting, managing, visualizing and exploring health and other data in many countries. The standard platform was designed to be suitable for compilation of TB data from recording and reporting systems that use either the 2006 or the 2013 versions of the WHO reporting framework, and can be used to conduct the analyses recommended in the WHO handbook for understanding and using TB data.

For the pilot workshop in west Africa, data entry focused on the first administrative level (e.g. province). However, the platform can also capture data at lower levels, such as districts or individual health facilities. Subnational population estimates, if available disaggregated by age and sex, can also be entered. This requires coordination with national census agencies, unless already available (as may be the case in countries using DHIS as their health management information system). Geographic information system (GIS) shape-files can also be imported into the platform, allowing for generation of maps for available surveillance indicators.

Examples of the analyses that can be generated are shown in Fig. B3.7.1.

The establishment of this DHIS2 platform could also provide the basis for prospective collection of aggregate-level data for countries still using a paper-based TB surveillance system or for countries that are in the process of transitioning to a national case-based TB surveillance solution.

The next multi-country workshop is scheduled for central and east African countries towards the end of 2016, and is expected to be followed by further workshops in other parts of the world.

a For further details, please see Background Document 2b prepared for the April 2016 meeting of the Task Force, available at www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/tf6_background_3b_drtb_burden.pdf?ua=1
b The 16 countries were Benin, Burkina Faso, Cape Verde, Gambia, Ghana, Guinea Conakry, Guinea Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Togo. They are part of the West Africa Research Network for TB that has been established by the Special Programme for Research and Training in Tropical Diseases (TDR).

c https://tbhistoric.org
d https://www.dhis2.org/
e http://apps.who.int/iris/bitstream/10665/69608/1/WHO_HTM_TB_2006.373_eng.pdf
SIM and SINAN case-based databases, followed by actions as appropriate to address gaps in detection, treatment or reporting.

### 3.6.3 TB case notification and treatment outcome data disaggregated by age, sex and location

Data on TB case notifications and the treatment outcomes of notified cases are routinely collected in most countries, and for the past decade about 200 countries and territories have reported national data to WHO in annual rounds of global TB data collection (Chapter 1 and Chapter 4). This has been facilitated by a standard recording and reporting framework that was first developed by WHO in the mid-1990s, with subsequent updates in 2006 and most recently in 2013.1 Most (98%) countries that reported 2015 notification data to WHO were able to disaggregate notifications of new and relapse (incident) cases by age and sex; these data are shown in Chapter 4 (see in particular Fig. 4.2) as well as in Annex 2 and Annex 4.

Notification and treatment outcome data for subnational areas are not routinely requested by WHO in annual rounds of global TB data collection. However, these data are usually available at country level and are a key source of information, including for TB epidemiological reviews and assessment of the performance of TB surveillance (Fig. 3.1). Moreover, as part of the WHO Global Task Force on TB Impact Measurement’s fifth strategic areas of work for 2016–2020 (Box 3.1), increased attention is being given to the analysis and use of subnational data. This has started with an initiative to provide a platform that allows safeguarding of subnational TB case notification and treatment outcome data for as many years as possible, while at the same time facilitating analysis and use of data to inform policy, planning, budgeting and resource mobilization. The platform has been built using the open source DHIS2 software,2 and its use was piloted as part of the preparations for and implementation of a regional workshop for 16 countries in West Africa in May 2016. Its use will be expanded to other countries later in 2016 and in 2017. Further details, including examples of the analyses that can be produced, are provided in Box 3.7.

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2 https://www.dhis2.org/
Chapter 4 :: Diagnosis and treatment: TB, HIV-associated TB and drug-resistant TB

KEY FACTS AND MESSAGES

In 2015, 6.4 million people with TB were notified to national TB programmes (NTPs) and reported to WHO. Of these, just over 6.1 million had an incident episode (new or relapse) of TB. The number of new and relapse TB cases notified and the notification rate per 100,000 population increased globally in 2013–2015, mostly explained by a 34% increase in notifications in India.

In 2015, 30% of the 3.4 million new bacteriologically confirmed and previously treated TB cases notified globally were reported to have had DST for rifampicin, with coverage of 24% for new TB patients and 53% for previously treated TB patients. Globally, 132,120 cases of multidrug-resistant TB or rifampicin-resistant TB (MDR/RR-TB) were detected and notified in 2015, and 124,990 were enrolled on treatment.

Despite increases in notifications of TB and MDR/RR-TB, big detection and treatment gaps remain. In 2015, the gap between notifications of new and relapse cases and the best estimate of the number of incident cases was 4.3 million, reflecting a mixture of underreporting of detected TB cases (especially in countries with large private sectors) and underdiagnosis (especially in countries where there are major geographic or financial barriers to accessing care). The gap between the number of MDR/RR-TB cases started on treatment and the number of notified cases estimated to have MDR/RR-TB was 205,000 (455,000 if compared with the estimated incidence of MDR/RR-TB).

From a global perspective, closing detection and treatment gaps requires progress in a particular subset of countries. Ten countries account for 77% of the total estimated gap between incidence and notifications, with India, Indonesia and Nigeria alone accounting for almost half of the total. Five countries account for over 60% of the gap between enrolments on MDR-TB treatment in 2015 and the estimated number of incident MDR/RR-TB cases in 2015: China, India, Indonesia, Nigeria and the Russian Federation.

The global male:female (M:F) sex ratio for notifications was 1.7, varying from 1.0 in Pakistan to 3.1 in Viet Nam among the high TB burden countries. Results from national TB prevalence surveys of adults show higher M:F ratios, indicating that notification data underestimate the share of the TB burden accounted for by men in some countries. Globally, children (aged <15 years) accounted for 6.3% of the new and relapse cases that were notified in 2015.

Globally in 2015, 55% of notified TB patients had a documented HIV test result, an 18-fold increase in testing coverage since 2004. In the African Region where the burden of HIV-associated TB is highest, 81% of TB patients had a documented HIV test result. The proportion of known HIV-positive TB patients on antiretroviral therapy (ART) was 78% globally, and above 90% in India, Kenya, Malawi, Mozambique, Namibia and Swaziland.

The only WHO-recommended rapid diagnostic test for detection of TB and rifampicin resistance currently available is the Xpert MTB/RIF® assay. The number of cartridges procured by countries eligible for concessional prices was 6.2 million in 2015, up from 550,000 in 2011. Of the 48 countries in at least one of the new lists of high burden countries, 15 had adopted national algorithms positioning Xpert MTB/RIF as the initial diagnostic test for all people suspected of having pulmonary TB by the end of 2015. These countries accounted for 10% of the estimated global number of incident TB cases in 2015.


At least 23 countries in Africa and Asia have introduced shorter regimens for treatment of MDR/RR-TB, which have achieved high treatment success rates (87–90%) under operational research conditions. A standardised shorter MDR-TB regimen of 9–12 months is now recommended in WHO guidance issued in May 2016 for all patients (excluding pregnant women) with pulmonary MDR/RR-TB that is not resistant to second-line drugs. As part of efforts to improve outcomes for MDR/XDR-TB, at least 70 countries had started using bedaquiline and 39 countries had used delamanid by the end of 2015.
Prompt and accurate diagnosis of tuberculosis (TB), HIV-associated TB and drug-resistant TB, followed by provision of treatment in line with international standards, prevents deaths and limits ill-health among people who develop the disease. It also prevents further transmission of infection to others. The 2020 and 2025 milestones for reductions in TB incidence and TB deaths set in the End TB Strategy (Chapter 2) require the case fatality ratio (the proportion of people with TB who die from the disease) to fall to 10% by 2020 and to 6.5% by 2025. The latter is only feasible if all those with TB are promptly diagnosed and effectively treated. Patient-centred care and prevention, backed by bold policies and supportive systems (including universal health coverage, UHC), are pillars one and two of the End TB Strategy (Box 4.1).

This chapter provides the latest data reported to WHO on the diagnosis and treatment of TB, HIV-associated TB and drug-resistant TB. Section 4.1 presents and discusses data for 2015 on notifications of TB cases and associated coverage of diagnostic testing, as well as trends since 2000. It includes data on the contribution of community engagement and public–public and public–private mix (PPM) initiatives to case-finding efforts in 2015. Section 4.2 focuses on treatment coverage (and detection and treatment gaps) for patients with TB, HIV-associated TB and drug-resistant TB, comparing numbers detected and treated with underlying estimates of disease burden (presented in more detail in Chapter 3). Section 4.3 provides the most recent data on treatment outcomes, for new and relapse TB patients, TB patients coinfected with HIV, and patients with multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB). It also contains information about the use of shorter MDR-TB regimens for treatment of MDR/RR-TB (i.e. RR-TB cases including those with MDR-TB) and the use of new anti-TB drugs for treatment of extensively drug-resistant TB (XDR-TB). Throughout the chapter, data are presented at global, regional and country levels, giving particular attention to high burden countries (HBCs). Further country-specific details for all of the indicators covered in this chapter are provided in Annex 2, Annex 4 and at http://www.who.int/tb/data.

4.1 Case notifications and testing coverage
4.1.1 TB case notifications and bacteriological confirmation

In 2015, 6.4 million people with TB were notified to national TB programmes (NTPs) and reported to WHO (Table 4.1).

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**Box 4.1**

**Pillars one and two of the End TB Strategy**

The first pillar of the End TB Strategy is “Integrated, patient-centred care and prevention”. It has four components:

- early diagnosis of TB including universal drug-susceptibility testing (DST), and systematic screening of contacts and high-risk groups;
- treatment of all people with TB including drug-resistant TB, and patient support;
- collaborative TB/HIV activities, and management of comorbidities; and
- preventive treatment of persons at high risk, and vaccination against TB.

The fourth component of the first pillar is the topic of Chapter 5.

The second pillar of the End TB Strategy is “Bold policies and supportive systems”. It has four components:

- political commitment with adequate resources for TB care and prevention;
- engagement of communities, civil society organizations, and providers of public and private care;
- UHC policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control; and
- social protection, poverty alleviation and actions on other determinants of TB.

The components of the second pillar are primarily discussed in Chapter 6.

For an overview of all aspects of the End TB Strategy, see Chapter 2 (Box 2.3).

Of these, just over 6.1 million had a new (incident) episode of TB (shown as the total of new and relapse cases), and an additional 227 873 had been previously diagnosed with TB but their treatment was changed to a retreatment regimen (and they were re-registered as a retreatment case). The number of new and relapse TB cases notified and the notification rate per 100 000 population increased between 2000 and 2009, then fell slowly until 2013, before increasing in 2013–2015 (Fig. 4.1). The increase since 2013 is mostly explained by increased notifications in India (+34% between 2013 and 2015), following the introduction of a national policy of mandatory notification, and the rollout of a nationwide web-based and case-based reporting system (called “Nikshay”) that facilitates reporting of detected cases by care providers in the public and private sectors. Further details about trends in notifications and comparisons with underlying estimates of TB incidence are provided in Section 4.2.1.
The distribution of notified cases in 2015 by age and sex is shown globally and for WHO regions in Fig. 4.2. The global male:female (M:F) sex ratio for notifications was 1.7. Among the 30 high TB burden countries, the ratio ranged from 1.0 in Pakistan to 3.1 in Viet Nam. Results from national TB prevalence surveys of adults show higher M:F ratios (for example, a M:F ratio of 4.5 in Viet Nam), indicating that notification data understate the share of the TB burden accounted for by men in some countries (see Section 3.6.1 in Chapter 3 for further details). Children (aged <15 years) accounted for 6.3% of the new and relapse cases that were notified globally. In the WHO Eastern Mediterranean, South-East Asia and Western Pacific regions, the TB epidemic is a markedly ageing one, with a progressive increase in the notification rate with age, and a peak among those aged ≥65 years. Elsewhere, and most noticeably in the WHO African Region, notification rates were highest among younger adults. In several eastern European countries as well as four high TB burden countries – China, Papua New Guinea, Thailand and Viet Nam – less than 2% of notified cases were children (Fig. 4.3). Variation among countries in the child:adult and M:F ratios of cases may reflect real differences in epidemiology, differential access to or use of reliable health care services, or differential reporting practices.

Extrapulmonary TB represented 15% of the 6.1 million incident cases that were notified, ranging from 8% in the WHO Western Pacific Region to 23% in the Eastern Mediterranea...
**FIG. 4.2**
New and relapse TB case notification rates by age and sex* in 2015, globally and for WHO regions

* Countries not reporting cases in these categories are excluded. Cases included make up 85% of reported cases.

**FIG. 4.3**
Percentage of new and relapse TB cases that were children (aged <15), 2015*

* 2014 data were used for 17 countries.
terranean Region. Of the 5.2 million new and relapse pulmonary TB patients notified globally in 2015, 3.0 million (57%) were bacteriologically confirmed (Table 4.1). The remaining patients were diagnosed clinically; that is, based on symptoms, chest X-ray abnormalities or suggestive histology. Although the percentage of cases with bacteriological confirmation worldwide has remained stable over the past 6 years, there have been improvements in the WHO African Region (56% to 64%), European Region (52% to 60%) and Region of the Americas (71% to 78%) (Fig. 4.4). In contrast, there was a fall (from 54% to 38%) in the WHO Western Pacific Region, influenced by a decline in bacteriological confirmation of notified cases in China in recent years.

There is considerable variation among countries in the percentage of new and relapse pulmonary TB patients that are bacteriologically confirmed (Fig. 4.5). Reasons for a low proportion of cases being bacteriologically confirmed should be assessed at country level, as should reductions over time. The microbiological detection of TB allows patients to be correctly diagnosed and started on the most effective treatment regimen as early as possible. Most clinical features of TB and abnormalities on X-ray or histology results generally associated with TB have low specificity, which may lead to false diagnoses of TB, and hence to people being enrolled on TB treatment unnecessarily.

PPM initiatives and schemes are integral components of national TB strategies, and have particular relevance to HBCs in Asia and Africa. The contribution of PPM to total notifications is shown in Table 4.2 for countries that have been collecting and reporting data for several years. In these countries, public–public mix interventions contributed 5–56% of total notifications in 2015, and public–private mix interventions contributed 6–48% of total case notifications.

4.1.2 HIV testing for TB patients and screening for TB among people living with HIV

In 2015, 3.4 million notified TB patients had a documented HIV test result, equivalent to 55% of notified TB cases. This represented an 18-fold increase in testing coverage since 2004, when WHO first requested countries to report data (Fig. 4.6). In 2015, the percentage of TB patients with known HIV status was highest in the WHO African Region (81%) and the Americas (82%). The level of testing in the 30 high TB/HIV burden countries averaged 64%, but varied considerably from 11% in Indonesia to above 75% in 18 countries (Fig. 4.7).

Globally, 15% of TB patients with an HIV test result were HIV-positive. Among WHO regions, the highest figure was in the African Region (36%). Overall, the percentage of TB patients testing HIV-positive has been falling globally since 2008 (Fig. 4.8). A total of 500 564 HIV-positive TB patients were reported by NTPs in 2015 (Table 4.1).

Systematic screening for TB among people living with HIV is recommended by WHO as an essential component of the HIV care package. In 2015, 86 countries reported

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\* A bacteriologically confirmed case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-recommended rapid diagnostic, such as Xpert MTB/RIF.
:: FIG. 4.5
Percentage of new and relapse pulmonary TB cases with bacteriological confirmation, 2015

:: TABLE 4.2
Contribution of public-public mix and public-private mix to notifications of TB cases in selected countries, 2015

Contribution of public-public mix to notifications of TB cases in selected countries, 2015

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>NUMBER OF TB CASES NOTIFIED BY NON-NTP PUBLIC SECTOR CARE PROVIDERS IN 2015</th>
<th>CONTRIBUTION OF NON-NTP PUBLIC SECTOR CARE PROVIDERS TO TOTAL CASE NOTIFICATIONS IN 2015 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>447 148</td>
<td>56</td>
</tr>
<tr>
<td>Egypt</td>
<td>1 375</td>
<td>17</td>
</tr>
<tr>
<td>India</td>
<td>284 636</td>
<td>16</td>
</tr>
<tr>
<td>Indonesia</td>
<td>61 183</td>
<td>18</td>
</tr>
<tr>
<td>Iran</td>
<td>7 196</td>
<td>69</td>
</tr>
<tr>
<td>Iraq</td>
<td>2 438</td>
<td>30</td>
</tr>
<tr>
<td>Nigeria</td>
<td>6 996</td>
<td>7.7</td>
</tr>
<tr>
<td>Philippines</td>
<td>79 197</td>
<td>28</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>4 575</td>
<td>48</td>
</tr>
<tr>
<td>Swaziland</td>
<td>312</td>
<td>6.8</td>
</tr>
<tr>
<td>Thailand</td>
<td>3 444</td>
<td>5.2</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>6 913</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Contribution of public-private mix to notifications of TB cases in selected countries, 2015

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>NUMBER OF TB CASES NOTIFIED BY PRIVATE SECTOR CARE PROVIDERS IN 2015</th>
<th>CONTRIBUTION OF PRIVATE SECTOR CARE PROVIDERS TO TOTAL NOTIFICATIONS IN 2015 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>60 879</td>
<td>29</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>15 195</td>
<td>11</td>
</tr>
<tr>
<td>India</td>
<td>184 802</td>
<td>11</td>
</tr>
<tr>
<td>Indonesia</td>
<td>30 550</td>
<td>9.2</td>
</tr>
<tr>
<td>Iran</td>
<td>3 019</td>
<td>29</td>
</tr>
<tr>
<td>Kenya</td>
<td>15 531</td>
<td>19</td>
</tr>
<tr>
<td>Malawi</td>
<td>3 049</td>
<td>18</td>
</tr>
<tr>
<td>Myanmar</td>
<td>23 513</td>
<td>17</td>
</tr>
<tr>
<td>Nigeria</td>
<td>13 088</td>
<td>14</td>
</tr>
<tr>
<td>Pakistan</td>
<td>72 144</td>
<td>22</td>
</tr>
<tr>
<td>Philippines</td>
<td>18 442</td>
<td>6.4</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>7 773</td>
<td>13</td>
</tr>
</tbody>
</table>

* Includes all contributions from non-NTP providers of care in the public sector, including public hospitals, public medical colleges, prisons/detention centres, military facilities, railways and public health insurance organizations.

* Private sector providers include private individual and institutional providers, corporate/business sector providers, mission hospitals, nongovernmental organizations and faith-based organizations.

2014 data were used for 15 countries.
**FIG. 4.6**
Percentage of new and relapse\(^\text{a}\) TB cases with documented HIV status, 2004–2015, globally and for WHO regions

\(^{a}\) The calculation is for all cases in years prior to 2015.

**FIG. 4.7**
Percentage of new and relapse TB cases with documented HIV status, 2015\(^{a}\)

\(^{a}\) Data for the Russian Federation are for new TB patients in the civilian sector only.
data about the number of TB cases notified from among those newly enrolled in HIV care (up from 59 countries in 2013 and 76 in 2014). In total, 231,637 (10%) of the almost 2.3 million people who were newly enrolled in HIV care in 2015 were notified as TB cases during the same year; data for the 12 high TB/HIV burden countries that reported data are shown in Table 4.3. Improvements in the coverage and quality of data for this indicator are necessary to track the impact of HIV care, especially antiretroviral therapy (ART), on the burden of TB in people living with HIV.

4.1.3 Rapid testing for TB

Use of rapid tests facilitates early detection of TB. One of the 10 priority indicators for monitoring implementation of the End TB Strategy (shown in Chapter 2, Table 2.1) is the percentage of new and relapse TB cases tested with a WHO-recommended rapid diagnostic (WRD) at the time of diagnosis. This and other indicators related to laboratory strengthening activities are part of the Framework of indicators and targets for laboratory strengthening under the End TB Strategy developed in 2016 (Box 4.2).

In this first year of reporting, 113 of 191 reporting countries and territories indicated that their routine surveillance system captures data on the percentage of new and relapse TB cases tested with a WRD at the time of diagnosis. However, further validation of the data as well as refinements to reporting systems are needed to improve data accuracy.

The only WRD currently available for detection of TB and rifampicin resistance is the Xpert MTB/RIF® assay (developed by Cepheid, USA). The original WHO recommendations in 2010 prioritized its use as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB, and most HBCs have adopted the original WHO recommendations into national policy (Table 4.4).

A policy update in 2013 expanded the recommended uses of the assay, to include its use for the diagnosis of TB in children, on selected specimens for the diagnosis of extrapulmonary TB, and for all people suspected of having pulmonary TB as a replacement for microscopy (conditional recommendations). A growing number of countries have already adopted national algorithms positioning Xpert MTB/RIF as the initial diagnostic test for all people suspected of having pulmonary TB. Among the 48 countries in one or more of three new lists of HBCs, 15 had adopted such algorithms by the end of 2015 (Table 4.4). In 2015, these 15 countries accounted for 11% of global notifications of pulmonary TB cases and 10% of the estimated global number of incident TB cases.

Between 2010 and 2015, a cumulative total of 4,672 GeneXpert instruments comprising 21,549 modules were procured in the public sector in 122 of the 145 countries eligible for concessional pricing. In 2015, 6.2 million test cartridges were procured by eligible countries, up from 550,000 in 2011. Of these, 45% (2.8 million) went to South Africa, but this percentage has fallen from a high of 63% in 2013, reflecting increasing adoption of the technology in other parts of the world. South Africa accounted for 20% of the total cumulative number of modules procured by the end of 2015.

Despite the significant scale-up in procurement of cartridges globally, installed instruments are still underused in many countries. Outside South Africa, the number of procured cartridges in 2015 compared to the total number of instrument modules reflects an average ratio of only 1.0 test per module per working day.
A well-equipped and staffed, quality-assured laboratory network with an efficient specimen referral system is an essential requirement for any NTP in the post-2015 era. Strengthening TB laboratories involves not only deploying modern diagnostics, but also ensuring widespread patient access with fast turnaround time and high-quality diagnosis.

A WHO Framework of indicators and targets for laboratory strengthening under the End TB Strategy was launched in 2016. It is intended to serve as a guide for all countries, with monitoring at global level on progress towards reaching targets. The indicators measure the capacity of programmes to detect patients accurately and rapidly using WRDs, provide universal DST, and ensure quality of testing at each level of the laboratory network.

Country capacity for diagnostic testing was previously monitored according to indicators and global targets describing numbers of microscopy centres per 100,000 population and culture/DST laboratories per 5 million population. These targets are no longer recommended, given the displacement of these technologies by new WRD technology in diagnostic algorithms and the need for country-specific targets considering epidemiology and patient access (urban or rural populations, specimen referral systems, etc.). Recommended methods for setting country-specific targets for numbers of tests and facilities* for each of the main diagnostic technologies – microscopy, WRDs (including Xpert MTB/RIF), culture and DST – have been developed, and are contained in an annex to the framework.

Ensuring quality of testing is critical for all diagnostic methods. A comprehensive external quality assessment (EQA) programme for smear microscopy should be implemented that includes slide rechecking or panel testing (or both), and regular supervision visits. Of the 150 countries and territories that reported data on the number of smear microscopy centres undergoing EQA in 2015, only 62 (41%) indicated the existence of a scheme that covered all centres in the country, with a further 21 (14%) covering at least 90% of centres. EQA programmes for Xpert MTB/RIF should include monitoring of key performance indicators (at least monthly, ideally using a remote monitoring system that receives data via a connectivity solution), panel testing and regular supervision visits; 54 of 114 reporting countries and territories (47%) indicated having a comprehensive scheme in 2015. Quality-assured DST is also important to ensure accurate detection of drug resistance to inform treatment decisions and to avoid false diagnoses. Of the 123 countries and territories globally reporting DST capacity, 73 (59%) indicated that all of their DST laboratories had demonstrated proficiency by panel testing in 2015. Establishing a comprehensive quality management system in laboratories allows for the necessary activities to be carried out at the right time and by the appropriately trained people; for the necessary equipment and consumables to be in stock; and for all manuals, guidelines, forms and standard operating procedures to be in place, so that processes are carried out correctly. In 2015, 78 of 153 responding countries and territories (51%) indicated having a comprehensive scheme towards achieving accreditation was being implemented in all laboratories conducting culture, line probe assays (LPAs) or DST.

As a key partner in strengthening the capacity and quality of TB diagnostic testing globally, the WHO TB Supranational Reference Laboratory (SRL) Network comprises 36 laboratories that provide a benchmark for proficiency testing, and can also provide long-term technical assistance to partner countries under the framework of collaborative agreements (Fig. B4.2.1). In 2016, the Centre for Tuberculosis at the National Institute for Communicable Diseases in Johannesburg, South Africa became the newest member of the network and the third SRL in the WHO African Region.

* The numbers of facilities by country in 2015 that were performing microscopy, Xpert MTB/RIF, culture, LPA, first and second line DST can be downloaded from http://www.who.int/tb/data/.
### TABLE 4.4
National guidance in place on use of Xpert MTB/RIF in high burden countries, 2015

<table>
<thead>
<tr>
<th>Country</th>
<th>High TB Burden (Yes)</th>
<th>High TB/HIV Burden (Yes)</th>
<th>High MDR-TB Burden (Yes)</th>
<th>National Policy Stipulating Xpert MTB/RIF as the Initial Diagnostic Test For:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All People Presumed to Have TB</td>
<td>People at Risk of HIV-Associated TB</td>
<td>People at Risk of Drug-Resistant TB</td>
<td>Children Presumed to Have TB</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>80%</td>
<td>93%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>23%</td>
<td>80%</td>
<td>97%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>83%</td>
<td>97%</td>
<td>80%</td>
</tr>
</tbody>
</table>

*The 48 countries shown in the table are the countries that are in one or more of the three lists of high TB, TB/HIV and MDR-TB burden countries (see also Chapter 2, Figure 2.3 and Table 2.2).*
Box 4.3
The WHO treatment guidelines for drug-resistant tuberculosis 2016 update

In May 2016, WHO revised its policy recommendations for the treatment of drug-resistant TB. The main changes in the 2016 recommendations were as follows:

- A shorter MDR-TB treatment regimen is now recommended for patients (other than pregnant women) with pulmonary RR or MDR-TB that is not resistant to second-line drugs.
- All RR-TB cases are to be treated with a MDR-TB regimen, regardless of isoniazid susceptibility.
- The design of longer MDR-TB regimens uses a different regrouping of component medicines, based on current evidence on their effectiveness and safety. Clofazimine and linezolid are now recommended as core second-line medicines in the MDR-TB regimen, whereas p-aminosalicylic acid is an add-on agent. Macrolides are no longer indicated for MDR-TB regimens.
- Specific recommendations are made on the treatment of children with MDR/RR-TB based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes.
- Evidence-informed recommendations on the role of partial resection surgery are now included.

No new evidence on the role of bedaquiline and delamanid was available at the time of the 2016 update and therefore no changes were made to the interim policy on the use of these new medicines. Both of these medicines have now been assigned to a specific subgroup of add-on agents.

The Global TB Programme in WHO is actively engaged with NTPs, technical and funding partners, the Global Drug-resistant TB Initiative (www.stoptb.org/wg/mdrtb/), the Global Laboratory Initiative (www.stoptb.org/wg/gli/) and Regional Green Light Committees to support countries to revise their national guidance, strengthen laboratory capacity, implement aDSM (see Box 4.2 and Box 4.6), and address barriers to the importation and use of new medicines and novel regimens.

4.1.4 Drug susceptibility testing and detection of drug-resistant TB

Drug-resistant TB threatens global TB control and remains a major public health concern in many countries. All RR-TB cases including those with MDR-TB are eligible for treatment with second-line medicines (Box 4.3). Cases of MDR-TB account for 83% of the worldwide total of MDR/RR-TB cases, with the proportion varying by region and country (e.g. from 67% to 91% among the WHO regions). Further details are provided in Chapter 3 (see in particular Table 3.5).

Universal access to DST, as called for in the End TB Strategy, can be defined as DST for at least rifampicin for all TB cases, plus DST for at least fluoroquinolones and second-line injectable agents among all TB cases with rifampicin resistance. DST methods include both phenotypic (conventional) and genotypic (molecular) testing methods. The most widespread technology currently available to test for drug resistance is Xpert MTB/RIF (see also Section 4.1.3), which can detect RR-TB.

Drug susceptibility testing for first-line drugs and detection of MDR/RR-TB

Progress in DST coverage since 2009, when WHO intensified efforts to track progress in the programmatic response to drug-resistant TB, is shown in Fig. 4.9. In 2015, 30% of the 3.4 million new bacteriologically confirmed and previously treated TB cases notified globally were reported to have had DST for rifampicin, with coverage of 24% for new TB patients and 53% for previously treated TB patients. These figures represent a small increase in DST coverage for rifampicin since 2014 (22% of new and previously treated TB cases) and major progress since 2009 (4.9%). The WHO European Region is the only part of the world where DST coverage has remained comparatively stable at a high level (about 60–70%; 69% in 2015). DST coverage varied substantially between countries, even within the same region, and among the 30 high MDR-TB burden countries (Fig. 4.10).

Globally, 132 120 cases of MDR/RR-TB were detected and notified in 2015 (Table 4.1). This was only a slight increase from 2014 (Fig. 4.11), although the aggregate global figure conceals country variation (Fig. 4.12). Between 2014 and 2015, the number of reported MDR/RR-TB cases increased by more than 20% in four of the 30 high MDR-TB burden countries (China, Nigeria, Philippines and Ukraine), but also fell by more than 20% in seven of those countries. The decline or stagnation in detection despite high

2 Frequently asked questions about the implementation of the new WHO recommendation on the treatment of the shorter MDR-TB regimen under programmatic conditions (http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regime.pdf).
**FIG. 4.9**
Percentage of bacteriologically confirmed TB cases tested for RR-TB, globally and for WHO regions, 2009–2015

*Among new laboratory confirmed and retreatment cases; test results in cases with previous history unknown not included. The abrupt increase in coverage in the African region in 2015 is largely due to improved differentiation by treatment history of reports from South Africa.*

**FIG. 4.10**
Percentage of bacteriologically confirmed TB cases tested for RR-TB, 2015

*Among new laboratory confirmed and retreatment cases; test results in cases with previous history unknown not included. Values for 2014 were used in countries without 2015 data by the reporting deadline.*
and increasing DST coverage could be due to more accurate reporting of laboratory test results (e.g. de-duplication of repeated counts of laboratory results for multiple specimens for the same individual patient) and other improvements to reporting of data. Wider use of electronic case-based systems to manage MDR-TB patient data could help to further improve the completeness and accuracy of reporting. By 2015, 23 of the 30 high MDR-TB burden countries reported that national case-based electronic registers were in place (16 of which covered all TB patients). These systems vary from surveillance databases to more elaborate clinical case-management registers with links to laboratory information systems.

The 132 120 MDR/RR-TB cases notified globally in 2015 (Table 4.1) amount to about 40% of the estimated total of 340 000 MDR/RR-TB cases that could have been detected had DST been provided to all pulmonary TB patients notified in 2015, and about 23% of the 580 000 estimated incident cases of MDR/RR-TB (uncertainty interval shown in [black]). The proportion of MDR/RR-TB cases estimated to exist among notified pulmonary cases varied from 21% to 64% in the six WHO regions. Among the 30 high MDR-TB burden countries, the proportion ranged from under 10% in the Democratic People’s Republic of Korea and Somalia to above 75% in Kazakhstan, Peru, South Africa and Ukraine (Fig. 4.12).

Evidence of progress in DST coverage notwithstanding, diagnostic DST must be further expanded to close detection gaps. Nine countries with more than 5000 notified TB cases in 2015 reported no capacity to perform phenotypic DST (Afghanistan, Burkina Faso, Chad, Congo, Papua New Guinea, Sierra Leone, Somalia, South Sudan and Yemen). Hence, there is a need for continued strengthening of laboratory capacity and wider uptake of new rapid diagnostics (Box 4.2, Box 4.4), as well as increased deployment of digital health technologies (especially “connected diagnostics”), to improve the completeness of reporting from laboratory and treatment centres.

WHO convened Guideline Development Groups in 2016 to review the evidence on the performance and utility of four TB diagnostic technologies. The following recommendations have been issued:

- For patients with confirmed rifampicin-resistant TB or MDR-TB, the Genotype® MTBDRsl (Hain LifeScience, Germany) second-line LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to fluoroquinolones and the second-line injectable drugs (conditional recommendation). This test allows quick triage of confirmed MDR/RR-TB patients into either the shorter MDR-TB regimen or the conventional longer regimen.

- Two new first-line LPAs – the MTBDRplus Version 2 (Hain LifeScience, Germany) and the Nipro NTM+MDRTB detection kit 2 (Nipro Corp., Japan) – demonstrated equivalence to the MTBDRplus Version 1 assay. These new LPAs are now also recommended for the detection of TB and for resistance to rifampicin and isoniazid.

- A molecular assay based on loop-mediated isothermal amplification (TB-LAMP), Loopamp™ MTBC Detection Kit (Eiken Chemical Company Ltd, Japan) may be used as a replacement for microscopy for the diagnosis of pulmonary TB in adults with signs and symptoms of TB (conditional recommendation). TB-LAMP may also be used as a follow-on test to microscopy in adults with signs and symptoms of pulmonary TB, especially when further testing of sputum smear-negative specimens is necessary.

Information about technologies in the pipeline is provided in Chapter 8. A comprehensive list of existing WHO policy documents on TB diagnostics is available at: [http://www.who.int/tb/areas-of-work/laboratory/policy_statements](http://www.who.int/tb/areas-of-work/laboratory/policy_statements).
Number of MDR/RR-TB cases detected (pink) and enrolled on MDR-TB treatment (green) 2009–2015 compared with estimated number of MDR/RR-TB cases among notified pulmonary TB cases in 2015 (uncertainty interval shown in red), 30 high MDR-TB burden countries.
Drug susceptibility testing for second-line drugs and detection of XDR-TB

Among MDR/RR-TB patients notified in 2015, 36% were reported to have had DST for both fluoroquinolones and second-line injectable agents. Coverage was lowest in the WHO Western Pacific and South-East Asia regions. In 2015, 7579 XDR-TB cases were reported to have been detected by 74 countries.

Treatment of XDR-TB patients was reported by 58 countries and territories (Fig. 4.13). Globally, 7234 patients with XDR-TB were enrolled on treatment (more than twice the level in 2014). Most of the cases in 2015 were notified by India (2130), Ukraine (1206), the Russian Federation (1205) and South Africa (719).

4.2 Treatment coverage

The Sustainable Development Goals (SDGs) include a target to “Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all” (Chapter 2, Box 2.2). Indicators for Target 3.8 of SDG3 include prevention and treatment coverage of tracer interventions, one of which is TB treatment.

TB treatment coverage is also one of the 10 priority indicators for monitoring progress in implementation of the End TB Strategy (Chapter 2, Table 2.1). This is because, as highlighted in the introduction to this chapter, universal coverage of appropriate diagnosis and treatment is a fundamental requirement for achieving the milestones and targets of the End TB Strategy. TB treatment coverage is defined as the number of new and relapse cases detected and treated in a given year, divided by the estimated number of incident TB cases in the same year, expressed as a percentage (Table 2.1). In this section, the number of notified new and relapse cases in 2015 is used as a proxy for the number of cases detected and treated. As discussed further below, however, there are also people with TB who are treated but not notified to national authorities (and in turn are not notified to WHO), and people who are notified but who may not be started on treatment.

ART is recommended for all HIV-positive TB patients, and a second-line MDR-TB treatment regimen is recommended for people with MDR/RR-TB. This section includes estimates of treatment coverage for these two interventions as well.

4.2.1 TB treatment coverage

Trends in notifications of new and relapse cases and estimated incidence are shown for the 30 high TB burden countries in Fig. 4.14. Estimates of TB treatment coverage in 2015 (calculated as notifications of new and relapse cases divided by estimated TB incidence) are shown globally, for WHO regions and the 30 high TB burden countries in Fig. 4.15. Globally, TB treatment coverage was 59% (range, 50–70%)2 in 2015, up from 54% (range, 46–65%) in 2010 and 36% (range, 30–43%) in 2000. Three WHO

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1 There are many different prevention and treatment interventions. In this context, a few interventions are selected to act as tracers for progress towards UHC for all interventions.

2 Here and elsewhere in the report, “range” refers to the 95% uncertainty interval.
Case notification rates (new and relapse cases, all forms) (black) compared with estimated TB incidence rates (green), 2000–2015, 30 high TB burden countries. Shaded areas represent uncertainty bands.

- Estimates of TB incidence for Bangladesh will be reviewed once final results from the 2015/2016 national TB prevalence survey are available.
- Estimates of TB incidence for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.
regions achieved higher levels of above 75%: the Region of the Americas, and the European and Western Pacific regions. Among the 30 high TB burden countries, the highest levels of treatment coverage in 2015 (>80%) were in Brazil, China, the Philippines and the Russian Federation. The lowest levels, with best estimates of 50% or less, were in the Democratic Republic of the Congo, Indonesia, Mozambique, Nigeria and the United Republic of Tanzania.

Globally in 2015, there was a gap of about 4.3 million cases between the 6.1 million new and relapse cases that were notified, and the estimated 10.4 million incident TB cases in the same year (Fig. 4.1). Although notifications have increased in recent years, especially in India (Section 4.1.1), the size of this gap is larger than indicated in previous global TB reports following an upward revision to estimated TB incidence in India for 2015 and previous years (for further details, see Chapter 3 and in particular Box 3.3). However, using the entire updated time-series of estimates of TB incidence as shown in Fig. 4.1, the global gap has been narrowing, especially in the WHO Eastern Mediterranean and Western Pacific regions, and to a lesser extent in the WHO South-East Asia Region.¹ Ten countries account for 77% of the total estimated gap between incidence and notifications (Fig. 4.16a), and India, Indonesia and Nigeria alone account for almost half of the total.

There are three main reasons for a gap between notifications and estimated incidence:

- **Underreporting of detected TB cases.** In many countries, especially those without policies on mandatory notification and other measures to ensure reporting of detected cases by all care providers and large private health sectors, levels of underreporting may be high.

- **Underdiagnosis of people with TB.** This can occur for reasons such as poor geographical and financial access to health care; failure to recognize TB signs and symptoms, and to test for TB when people do present to health facilities; and diagnostic tests that are not good enough to ensure accurate identification of all cases.

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¹ Time trends in countries and regions are shown in Annex 2 and Annex 3, respectively.
The ten countries with the largest gaps between notifications of new and relapse (incident) TB cases and the best estimates of TB incidence, 2015:


Estimates of TB incidence for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.

The ten countries, ranked in order of the size of the gap between notified cases and the best estimate of TB incidence in 2015, are India, Indonesia, Nigeria, Pakistan, South Africa, Bangladesh, DR Congo, China, UR Tanzania and Mozambique. Estimates of TB incidence for India are interim in nature, pending results from the national TB prevalence survey planned for 2017/2018.

The ten countries, ranked in order of the size of the gap between the number of patients started on treatment for MDR-TB and the best estimates of MDR/RR-TB incidence, 2015:


The ten countries, ranked in order of the size of the gap between number of patients started on MDR-TB treatment and the best estimate of MDR/RR-TB incidence in 2015, are India, China, Russian Federation, Indonesia, Nigeria, Pakistan, Philippines, Ukraine, Myanmar and DR Congo.
Overestimation of the level of TB incidence. In this report, estimates of TB incidence for 74 countries with 22% of the world’s estimated cases are based on expert opinion about levels of underreporting and underdiagnosis, as opposed to direct measurements from surveillance or survey data (Chapter 3). Also, the uncertainty intervals around the best estimates of TB incidence can be wide, and gaps may be lower or higher than the best estimates quoted in this section.

In some of the countries with the largest estimated gaps between notifications and TB incidence there is already evidence about the reasons for such gaps, and actions to address them are being taken or are planned. In India, various data sources point to large underreporting of detected TB cases (see also Chapter 3, Box 3.3). These include two studies of sales of anti-TB drugs in the private sector; the recent upsurge in notifications that followed a national policy of mandatory notification, as well as efforts to increase engagement with all care providers and to facilitate reporting via a national web-based reporting system; and comparison of household survey data on self-reported TB treatment with notification data in the same survey areas. In Indonesia, the 2013–2014 national TB prevalence survey showed high levels of underreporting of detected TB cases, leading to recommendations such as a mandatory policy on notification and intensified engagement with public and private hospitals where many people with TB were being treated. In Nigeria, the 2012 prevalence survey found that 75% of the smear-positive cases detected had symptoms that met national screening criteria, but had not been previously diagnosed, demonstrating high levels of underdiagnosis and a need to strengthen access to diagnostic and treatment services.

In countries where underreporting is thought to exist, inventory studies in which electronic lists of notified cases are compared with electronic lists of TB cases detected by all care providers, ideally employing unique identifiers, can be used to quantify levels of underreporting. Such studies have already been used to inform estimates of TB incidence in several countries (Chapter 3), and are planned or under way in China, Indonesia (as a follow-on from the levels of underreporting indicated by the 2013–2014 national TB prevalence survey), Nigeria (metropolitan Lagos), the Philippines and Viet Nam. When these studies are done prospectively (as opposed to retrospectively using electronic databases that are already available), the mapping of providers that is required at the beginning can subsequently help with efforts to engage all care providers, including in reporting.

Examples of mechanisms to ensure reporting of all detected cases include linking reimbursement from health insurance schemes to notification of cases (as in the Republic of Korea), linking the supply of first-line drugs to notification of cases (as in Brazil), facilitating reporting via online web-based systems with limited data entry requirements (as in India), and wider implementation of PPM schemes and initiatives (Table 4.2). Even in the countries shown in Table 4.2, PPM implementation is often not nationwide, and its contribution to notifications may come from a small proportion of providers that willingly collaborate with NTPs, or from parts of the country only. In India, for example, the big increase in notifications that occurred in 2013–2015 was from a small subset of districts. Chapter 6 provides further discussion of PPM, including the role of a whole-of-government approach, and innovative approaches to engaging private practitioners that are being tested in Bangladesh, India, Indonesia, Pakistan and Myanmar.

Recent national TB prevalence surveys have also shown that, in both Africa and Asia, detection and reporting gaps are systematically higher for men than for women (for further details, see Section 3.6.2 in Chapter 3). This suggests that specific efforts are needed to improve access to TB diagnosis and treatment for men.

Systematic screening for active TB among specific populations can also help to ensure early diagnosis and reduce levels of underdiagnosis. WHO recommends such screening for contacts of bacteriologically confirmed cases, people living with HIV and people exposed to silica dust (see also Chapter 5). Other individuals at risk should be considered for systematic screening based on an assessment of TB epidemiology in each setting. To date, there have been few assessments of the implementation and outcomes of systematic screening in countries that are currently introducing or scaling up systematic screening. However, this is expected to become a more prominent part of national programme monitoring and evaluation efforts in future. Engaging communities could also add value to efforts to improve case detection and patient support (Box 4.5).

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4 www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/t6_p06_prevalence_surveys_2009_2015.pdf


6 For this reason, the data requested in WHO’s annual round of global TB data collection focus on screening among people living with HIV and close contacts. These data are presented in Chapter 5.
Community contributions to TB notifications and treatment support

Engagement of communities, nongovernmental and civil society organizations is at the heart of the End TB Strategy. Community-based TB activities cover a wide range of activities that contribute to the detection, referral and treatment of people with drug-susceptible, drug-resistant and HIV-associated TB. They are conducted outside the premises of formal health facilities (e.g. hospitals, health centres and clinics) in community-based structures (e.g. schools, places of worship, congregate settings and markets) and homesteads. Community health workers and community volunteers carry out community-based TB activities. They can be part of the public health services or nongovernmental or other civil society organizations. ENGAGE-TB is an approach to integrating community-based TB activities into the work of these organizations.

Of the 114 countries that were asked to respond to questions about the contributions of communities to TB notifications and treatment support in WHO’s 2016 round of global TB data collection, 49 reported data for at least one indicator. Of the 49 countries, 60% (29/49) reported nationwide coverage of community engagement in case notification or community-based treatment support (Fig. B4.5.1). 40 out of 49 countries (82%) reported data on the contribution of community referrals to TB notifications; 41 out of 49 (86%) reported on the proportion of TB patients receiving community-based treatment support; and 34 out of 49 (69%) reported information about the treatment success rate among TB patients who received treatment support in the community.

There are many countries in which community-based TB activities are a routine component of TB services, but where it is not yet possible to quantify this contribution. Of the 65 (out of 114) countries that were asked to report but did not submit any data on notifications, more than half (33/65) nonetheless stated that community-based activities are implemented. In these 33 countries, the mean coverage of community-based activities is 79% of basic management units while a total of 19 countries reported countrywide implementation of community-based activities. Efforts to support countries to incorporate community engagement indicators into their routine monitoring and evaluation systems continue.

4.2.2 Treatment coverage of antiretroviral therapy for HIV-positive TB cases

WHO recommends ART for all HIV-positive TB patients within the first 8 weeks of starting TB treatment.1 The number of notified HIV-positive TB patients on ART has grown in recent years (Fig. 4.8, Fig. 4.17) and reached 390,630 in 2015, equivalent to 78% of the 500,564 notified TB patients known to be HIV-positive (Table 4.1). This was an increase from 36% in 2005, when data on provision of ART to HIV-positive TB patients were first collected at global level.2 In the 30 high TB/HIV burden countries, 80% of the TB patients known to be HIV-positive were on ART and in six of these countries (India, Kenya, Malawi, Mozambique, Namibia and Swaziland) the figure was more than 90%.


2 There may be discrepancies in data on provision of ART to HIV-positive TB patients that are reported by national TB programmes and national HIV programmes. These discrepancies have reduced in recent years and are mostly resolved through follow-up and validation efforts.
Number of new and relapse cases known to be HIV-positive (black) and number started on ART (blue) compared with estimated number of incident HIV-positive TB cases (red), 2004-2015, 30 high TB/HIV burden countries

* The calculation is for all cases in years prior to 2015.
In contrast, there were nine high TB/HIV burden countries (Brazil, Chad, China, Congo, Ghana, Guinea-Bissau, Indonesia, Liberia, and Myanmar) in which less than 50% of HIV-positive TB patients were started on ART in 2015. ART treatment coverage for people with TB can also be assessed by comparing the number of HIV-positive TB patients on ART with the estimated number of HIV-positive incident TB cases (Fig. 4.18). This comparison reveals larger gaps. Globally in 2015, the number of HIV-positive TB patients on ART was 33% of the estimated global number of incident HIV-positive TB cases. There was considerable variation among the high TB/HIV burden countries and only four achieved ART coverage of more than 50% (Kenya, Namibia, Swaziland and Uganda). Improvements are needed in the detection of TB among HIV-positive people, the coverage of HIV testing among TB patients, and the enrolment of HIV-positive TB patients on ART.

### 4.2.3 Treatment coverage for MDR/RR-TB

Trends in the number of patients enrolled on MDR-TB treatment globally and in the 30 high MDR-TB countries since 2009 are shown in Fig. 4.11 and Fig. 4.12. The number of people enrolled on treatment globally was 124,990 in 2015, an increase of 13% from 110,587 in 2014. There was a 14% increase in enrolments between 2014 and 2015 in the 30 high MDR-TB burden countries, with increments amounting to more than 1000 patients in China, India, the Philippines, the Russian Federation and Ukraine.

Globally, the 124,990 patients starting second-line MDR-TB treatment in 2015 represented about 37% of the 340,000 MDR/RR-TB cases estimated to have existed among pulmonary TB patients notified in 2015 (Fig. 4.19), and 20% of the incidence estimate (Fig. 4.11). Five countries accounted for over 60% of the gap between enrolments on MDR-TB treatment in 2015 and the estimated number of incident MDR/RR-TB cases in 2015: China, India, Indonesia, Nigeria and the Russian Federation (Fig. 4.16b).

The number of cases starting MDR-TB treatment in 2015 was equivalent to 95% of the 132,120 MDR/RR-TB patients notified in that year (Table 4.1). The ratio exceeded 90% in 19 high MDR-TB burden countries, and the WHO European and South-East Asian regions, and was lowest in the...
African Region (Fig. 4.19). In 2015, enrolments outstripped notifications of MDR/RR-TB in eight high MDR-TB burden countries (Fig. 4.12). This may be caused by empirical treatment of TB patients considered at risk of having MDR/RR-TB but for whom a laboratory-confirmed diagnosis was missing, incomplete reporting of laboratory data, or enrolment of “waiting lists” of people with MDR/RR-TB who were detected before 2015.

The ratio of enrolled to diagnosed cases was below 60% in two high MDR-TB burden countries in 2015: China (59%) and Nigeria (53%). These low ratios show that progress in detection is far outstripping capacity to provide treatment; they may also reflect weaknesses in data collection systems. Treatment coverage will not improve globally unless there is an intensification of efforts in the countries with the largest burden, particularly China and the Russian Federation, but also India where the rate of increase in enrolments has slowed.

In many countries, one of the reasons for inadequate access to treatment of drug-resistant TB is that the network for the programmatic management of drug-resistant TB (PMDT) is too centralized. Hospital-based models of care continue to dominate in many countries, and hold back wider use of decentralized ambulatory care, a change of direction that could expand population access to PMDT (see also Chapter 6). In addition, gaps for palliative and end-of-life care are evident. In 2015, only 34 countries (including 16 of the 30 high MDR-TB burden countries) reported that such services were provided within the scope of their NTPs.

4.3 Treatment outcomes
This section highlights the latest results of treatment for people who started TB treatment on a first-line regimen in 2014, and people that started a second-line regimen for MDR/RR-TB in 2013.

4.3.1 Treatment outcomes for new and relapse TB patients
The definitions of TB treatment outcomes for new and relapse cases of TB that are recommended by WHO are provided in an updated recording and reporting framework
issued in March 2013 and updated in 2014. Most new and relapse cases do not have MDR/RR-TB; however, in some parts of the world, especially countries of the former Soviet Union, more than 20% of new and relapse cases do so (Chapter 3). Universal access to DST is required to ensure that all people with TB receive appropriate treatment, as discussed in Section 4.1.

Data on treatment outcomes in 2014 for new and relapse cases of TB are shown for the world, the six WHO regions and the 30 high TB burden countries in Fig. 4.20, and trends globally and in the six WHO regions since 2000 are shown in Fig. 4.21. Globally, the treatment success rate for the 5.9 million new and relapse cases that were treated in the 2014 cohort was 83%. This was a reduction from 87% for the 2013 cohort, which can be explained by data for India. From 2013 to 2014, there was a big increase in notifications of TB cases in India (see also Section 4.1.1) from the private sector. However, while the total number of TB patients reported as successfully treated also increased in India, there was an increase in the percentage of TB patients for whom the treatment outcome was categorized as “not evaluated” (17%). As a consequence, the overall treatment success rate fell from 86% to 74%, and the impact is large enough to be evident in the aggregated data for 2014 for the world and the WHO South-East Asia Region (Fig 4.21). The NTP in India has been taking actions to improve reporting of treatment outcomes from private sector providers, including by facilitating reporting of outcomes via the national web-based reporting system known as Nikshay, and the aim is to achieve complete reporting of outcomes from the private sector by 2017. Of note, when the 2014 data for India are restricted to the same providers/facilities, the treatment success rate remains comparable to 2013, at 87%. When India is excluded from global calculations, the treatment success rate is 86%.

Among the six WHO regions, the highest treatment success rates in 2014 were in the Western Pacific Region (92%) and the Eastern Mediterranean Region (91%), and the lowest (at 76%) were in the Region of the Americas (due to high levels of loss to follow up and missing data) and the European Region (due to high rates of treatment failure and death, influenced by the high frequency of MDR/RR-TB). Only eight of the 30 high TB burden countries had reached or exceeded a 90% treatment success rate, although the validity of treatment outcome data was not always ascertained. In several high TB burden countries, the completeness of outcome reporting was low. In the Central African Republic, Congo, Liberia and Papua New Guinea, loss to follow-up exceeded 15%, whereas in Angola, Congo, India and Lesotho more than 10% of cases were unevaluated. In Brazil (71% success), 21% of cases were either lost to follow-up or their treatment outcome was missing.

Despite the decrease in the overall treatment success rate, the specific situation in each country is different at the beginning of 2016. In the six WHO regions, the highest treatment success rates in 2014 were in the Western Pacific Region (92%) and the Eastern Mediterranean Region (91%), and the lowest (at 76%) were in the Region of the Americas (due to high levels of loss to follow up and missing data) and the European Region (due to high rates of treatment failure and death, influenced by the high frequency of MDR/RR-TB). Only eight of the 30 high TB burden countries had reached or exceeded a 90% treatment success rate, although the validity of treatment outcome data was not always ascertained. In several high TB burden countries, the completeness of outcome reporting was low. In the Central African Republic, Congo, Liberia and Papua New Guinea, loss to follow-up exceeded 15%, whereas in Angola, Congo, India and Lesotho more than 10% of cases were unevaluated. In Brazil (71% success), 21% of cases were either lost to follow-up or their treatment outcome was missing.

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rate, the absolute number of TB patients reported to have been successfully treated has continued to increase over time, both globally and in all WHO regions (Fig. 4.21).

### 4.3.2 Treatment outcomes for new and relapse TB patients coinfected with HIV

In the 2016 round of global TB data collection, 106 countries (which collectively accounted for 80% of the HIV-positive TB patients reported by NTPs in 2014) reported treatment outcomes for the 2014 patient cohort disaggregated by HIV status. This included 19 of the 30 high TB/HIV burden countries. Treatment outcomes for these countries, as well as the six WHO regions and globally, are shown in Fig. 4.22. Overall, the treatment success rate in 2014 was worse for HIV-positive TB patients (75%) than for HIV-negative TB patients (83%). There were particularly large differences in the Region of the Americas, the Eastern Mediterranean and the Western Pacific regions, where the treatment success rates for HIV-positive TB patients were 56%, 53% and 72% respectively, compared with 77%, 82% and 93% respectively among HIV-negative patients.

Globally, the proportion of TB patients who died during treatment was about four times higher among HIV-positive TB patients (11% versus 3%). In WHO regions the relative difference was lowest in the African Region (10% versus 5%) and highest in the Western Pacific Region (15% versus 2%).

Reasons for the comparatively poor outcomes of HIV-positive TB patients include late detection of HIV-associated TB and delays in starting ART or TB treatment. To reduce excessive TB mortality in HIV-positive people, WHO recommends routine HIV testing among presumptive and diagnosed TB cases and TB screening among people living with HIV, early ART and provision of TB preventive treatment. WHO recently published a revised algorithm for clinical management of HIV-positive people who are seriously ill and suspected of having TB. 1

### 4.3.3 Treatment outcomes for TB patients with MDR/RR-TB and XDR-TB

A total of 127 countries and territories reported treatment outcomes for people started on MDR-TB treatment in 2013. The number of cases reported in annual cohorts has steadily increased over time, reaching 86,936 cases globally in the 2013 cohort, a 17% increase over the previous year (Fig. 4.23).

Overall, the proportion of MDR/RR-TB patients in the 2013 cohort who successfully completed treatment (i.e. cured or treatment completed) was 52%: 17% died, 15% were lost to follow-up, 9% were determined to be treatment failure and 7% had no outcome information. The treatment success rate was highest in the WHO Eastern

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Mediterranean Region (68%), and lowest in the South-East Asia Region (49%). In the 2013 cohort, treatment failure was highest in the WHO European Region (13%), and the death rate was highest in the African and South-East Asia regions (21%). Loss to follow-up was highest in the WHO Region of the Americas (25%).

Despite the low levels of treatment success, over 150,000 people who started MDR-TB treatment globally between 2007 and 2013 were reported to have completed their treatment successfully. Among the 30 high MDR-TB burden countries, the Democratic Republic of Korea, Kenya, Myanmar, Nigeria, and Somalia reported >75% treatment success among the MDR/RR-TB cohorts enrolled in 2013. Conversely, treatment success was <50% in countries with the largest cohorts: India, the Philippines, the Russian Federation, South Africa and Ukraine. This was primarily due to high death rates in India, South Africa and Ukraine; high treatment failure rates in the Russian Federation and Ukraine; and high rates of loss to follow up or missing data in India, the Philippines and South Africa. Data on treatment outcomes for MDR/RR-TB patients were not reported by Papua New Guinea and Thailand.

Among 4086 XDR-TB patients started on treatment in 2013 in 47 countries and for whom outcomes were reported, 28% completed treatment successfully, 27% died, treatment failed for 21%, and 23% were lost to follow-up or not evaluated.
Countries that had used shorter MDR-TB treatment regimens by the end of 2015

Countries that had used bedaquiline and/or delamanid for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of 2015

Data shown reflects country reports supplemented with additional information from pharmaceutical manufacturers.
**Box 4.6**

**Active TB drug-safety monitoring and management**

aDSM is the active and systematic, clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens, to detect, manage and report suspected or confirmed drug toxicities. The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second-line treatment for drug-resistant TB and to generate standardized data to inform future policy updates on the use of such medicines.

aDSM includes three essential activities to achieve these objectives:

- Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and adverse events (AEs). Proposed schedules have been developed for use in patients on shorter regimens or on new medications.

- All AEs detected should be managed in a timely manner, to deliver the best possible patient care. Management of AEs is beyond the scope of this document, and further details are provided in other implementation documents.

- Standardized data should be systematically collected and reported for any detected serious adverse event (SAE). These data will eventually be used to characterize the types of SAEs, assess the safety of the treatment, and inform future policy on the use of these medicines.

In 2015, 51 of the 140 countries that enrolled patients on MDR-TB treatment (including 15 of the 30 high MDR-TB burden countries) reported AEs in least one patient.

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Chapter 5 :: TB prevention services

KEY FACTS AND MESSAGES

Prevention of new infections of *Mycobacterium tuberculosis* and their progression to tuberculosis (TB) disease is critical to reduce the burden of disease and death caused by TB, and to achieve the End TB Strategy targets set for 2030 and 2035.

Current health interventions for TB prevention are: treatment of latent TB infection (LTBI), with particular attention to children aged under 5 years who are household contacts of bacteriologically confirmed pulmonary TB cases, and people living with HIV; prevention of transmission of *Mycobacterium tuberculosis* through infection control; and vaccination of children with the Bacille-Calmette-Guérin (BCG) vaccine.

Globally in 2015, there were an estimated 1.2 million children aged under 5 years who were household contacts of bacteriologically confirmed pulmonary TB cases and who were eligible for TB preventive treatment according to current policy recommendations. In comparison, only 87 236 children in this age group (7.1%) were reported to have been started on TB preventive treatment in 2015, based on data from 88 countries.

A total of 910 124 people who were newly enrolled in HIV care were started on TB preventive treatment in 2015, based on data from 58 countries. This was a large increase from negligible levels in 2005, when WHO first requested data. South Africa accounted for the largest share (45%) of the total in 2015, as in previous years, followed by Malawi, Mozambique and Kenya. Ten countries reported data for the first time, including Kenya.

Despite progress in providing TB preventive treatment to people living with HIV, much more remains to be done. Of the 30 high TB/HIV burden countries, 21 did not report any provision of preventive treatment in 2015. In the nine high TB/HIV burden countries that did report data, coverage among people newly enrolled in HIV care ranged from 2% in Indonesia to 79% in Malawi.

There is a need to improve initiation, completion and reporting of TB preventive treatment for other at-risk populations, including clinical risk groups such as patients with silicosis, patients starting anti-tumour necrosis factor (TNF) therapy and patients preparing for organ transplantation.

The ratio of the TB notification rate among health-care workers to the TB notification rate in the general adult population is a good indicator of the impact of TB infection control in health facilities. In 2015, 9977 health-care workers were reported with TB from 67 countries; China accounted for 30% of these cases and South Africa for 21%. In 16 countries, the number of TB cases per 100 000 health-care workers was more than double the notification rate in the general adult population.

BCG vaccination should be provided as part of national childhood immunization programmes according to a country’s TB epidemiology. In 2015, 163 countries reported providing BCG vaccination as a standard part of these programmes, of which 102 reported coverage of above 90%.

Monitoring and evaluation of TB prevention services is challenging given the lack of systems for recording and reporting data, and the involvement of multiple service providers. In 2016, WHO developed standard indicators to monitor and evaluate the provision of TB preventive treatment. Countries are encouraged to adopt these indicators and an electronic surveillance system that facilitates collection and analysis of the relevant data.

Development and expanded use of shorter regimens for TB preventive treatment, which require a smaller number of doses and are associated with fewer adverse events, will facilitate implementation at a larger scale. Innovative diagnostic tests with improved performance and predictive value are needed to target individuals who will benefit most from TB preventive treatment.
Prevention of new infections of Mycobacterium tuberculosis and their progression to TB disease is critical to reduce the burden of disease and death caused by TB, and to achieve the End TB Strategy targets set for 2030 and 2035. The targets of an 80% reduction in TB incidence by 2030 and a 90% reduction by 2035, compared with 2015, require an historically unprecedented acceleration in the rate at which TB incidence falls after 2025 (Chapter 2). This can only happen if the probability of progression from latent TB infection (LTBI) to active TB disease among the 2–3 billion people already infected worldwide is reduced below the current lifetime risk of 5–15%.1 In some low-burden countries, reactivation accounts for about 80% of new cases of disease.2,3 Interventions that could result in a much greater reduction include more effective treatments for LTBI and a new vaccine capable of preventing reactivation of LTBI in adults.

There are three major categories of health interventions currently available for TB prevention:

- treatment of LTBI — through isoniazid daily for 6 or 9 months, or isoniazid plus rifampicin daily for 3–4 months, or rifampicin daily for 3–4 months or isoniazid plus rifapentine once a week for 3 months — with particular attention to children aged under 5 years who are household contacts of TB cases with bacteriologically confirmed pulmonary disease, and people living with HIV (Section 5.1);
- prevention of transmission of Mycobacterium tuberculosis through infection control (Section 5.2); and
- vaccination of children with the Bacille-Calmette-Guérin (BCG) vaccine (Section 5.3).

The three main sections of this chapter present and discuss the status of progress in provision of these services. Particular attention is given to countries in the lists of 30 high TB burden and 30 high TB/HIV burden countries (Chapter 2).

5.1 Treatment of latent TB infection

LTBI is defined as a state of persistent immune response to Mycobacterium tuberculosis without clinically-manifested evidence of active TB disease. There are two particular risk groups for whom specific efforts to diagnose and treat LTBI are recommended by WHO: children aged under 5 years who are household contacts of pulmonary TB cases, and people living with HIV.4 Coverage of contact investigation and treatment of LTBI among child contacts and people living with HIV are in the top-10 list of indicators for monitoring implementation of the End TB Strategy, with a target of over 90% coverage by 2025 at the latest (Chapter 2, Table 2.1).

Data on provision of TB preventive treatment for people living with HIV have been collected for more than 10 years. However, until 2016 there was no standardized global guidance on how to monitor the coverage of preventive treatment among child contacts or other high-risk groups. Such guidance has now been developed by a WHO Global LTBI Task Force,5 and the recommended indicators are shown in Table 5.1. The rest of this section discusses findings from data gathered from countries and territories in WHO’s 2016 round of global TB data collection about TB preventive treatment for the three risk groups.

5.1.1 Child contacts under 5 years of age who are household contacts of TB cases

In 2015, of the 189 countries that reported at least one notified bacteriologically confirmed pulmonary TB case, 88 (47%) reported data about the number of contacts aged under 5 years who were started on TB preventive treatment (Fig. 5.1). A total of 87,236 child household contacts were initiated on TB preventive treatment (Table 5.2), with the largest numbers reported by the WHO African Region (28% of the global total) and Eastern Mediterranean Region (20% of the global total). At country level, Afghanistan reported the largest number (10,164) followed by Bangladesh (9833). Only nine of the 30 high TB burden countries reported data. A few countries in the WHO European Region noted that it was not possible to report data for children specifically because preventive treatment is provided to adults as well as children; this may also apply to some low TB burden countries that did not report data. Thus, the data reported to WHO underestimate the actual number of children who were started on TB preventive treatment.

Comparisons of the number of children started on treatment for LTBI in 2015 with national estimates of the number of children aged under 5 years who were contacts of bacteriologically confirmed pulmonary TB cases and eligible for TB preventive treatment are also shown in Table 5.2. Globally, the 87,236 children started on TB preventive treatment in 2015 represented 7.1% (range, 6.9–7.4%) of the 1.2 million (range, 1.18 million to 1.26 million) children estimated to be eligible for it. Higher levels of coverage were achieved in the WHO Region of the Americas (best estimate 67%; range, 63–71%) followed by the European Region (best estimate 42%; range, 40–44%). In the high TB or TB/HIV burden countries that reported data, coverage ranged from 2.6% in Cameroon to 41% in Malawi.

5.1.2 People living with HIV

There has been a considerable increase in the provision of preventive TB treatment in recent years, especially in

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5 http://www.who.int/tb/challenges/task_force/en/
**TABLE 5.1.**

Summary of monitoring and evaluation indicators for LTBI programmatic management recommended by WHO

<table>
<thead>
<tr>
<th>COUNTRY GROUP</th>
<th>AT RISK POPULATIONS WITH STRONG RECOMMENDATIONS</th>
<th>CORE GLOBAL AND NATIONAL INDICATORS</th>
<th>CORE NATIONAL INDICATORS</th>
<th>OPTIONAL INDICATORS</th>
</tr>
</thead>
</table>
| LOW TB BURDEN | 1) People living with HIV.  
2) Adults and children who are household contacts of pulmonary TB cases.  
3) Clinical indications: patients with silicosis; patients initiating anti-tumour necrosis factor (TNF) treatment; patients on dialysis; patients preparing for organ or haematologic transplantation. | 1) Proportion of children less than 5 years old who are household TB contacts (according to national guidelines) who have completed TB investigations  
2) Proportion of children under 5 years old who are household TB contacts (according to national guidelines) who are eligible for starting on TB preventive therapy that have started treatment  
3) Proportion of eligible people living with HIV newly enrolled in HIV care, started on TB preventive therapy | 1) Proportion of eligible individuals from at risk populations (according to national guidelines) tested for latent TB infection.  
2) Proportion of individuals from at risk populations (according to national guidelines) with a positive latent TB test who are eligible for starting TB preventive therapy that have started treatment.  
3) Proportion of individuals from at risk populations (according to national guidelines) with a positive latent TB test who have started on TB preventive therapy that have completed the course. | 1) TB incidence rate among risk populations (as defined by national guidelines). |
| HIGH TB BURDEN | 1) People living with HIV.  
2) Children under 5 years of age who are household contacts of pulmonary TB cases. | 1) Proportion of eligible people living with HIV who completed a course of TB preventive therapy.  
2) Proportion of children less than 5 years old who are household TB contacts (according to national guidelines) who have completed a course of TB preventive therapy. | | |

**FIG. 5.1**

Availability of data on the number of children aged <5 years who were household contacts of bacteriologically confirmed pulmonary TB cases and were started on TB preventive treatment, 2015
**TABLE 5.2**

TB preventive treatment in 2015 for people living with HIV and children under 5 years of age who were household contacts of a bacteriologically confirmed pulmonary TB case, 16 high TB or TB/HIV burden countries that reported data, WHO regions and globally

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of people living with HIV newly enrolled in care (A)</th>
<th>People newly enrolled in HIV care who were started on TB preventive treatment in 2015</th>
<th>Estimated number of children under 5 years of age who were household contacts of a notified bacteriologically confirmed pulmonary TB case, and eligible for TB preventive treatment, in 2015 (C)</th>
<th>Children under 5 years of age who were started on TB preventive treatment in 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>—</td>
<td>—</td>
<td>45 000 (41 000–49 000)</td>
<td>9 833 (20–24)</td>
</tr>
<tr>
<td>Cambodia</td>
<td>3475</td>
<td>868 25</td>
<td>5100 (4600–5500)</td>
<td>731 (13–16)</td>
</tr>
<tr>
<td>Cameroon</td>
<td>—</td>
<td>—</td>
<td>11 000 (10 000–13 000)</td>
<td>298 (2.4–2.8)</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>37 600</td>
<td>17 585 47</td>
<td>31 000 (28 000–34 000)</td>
<td>—</td>
</tr>
<tr>
<td>Indonesia</td>
<td>29 893</td>
<td>591 2.0</td>
<td>67 000 (61 000–73 000)</td>
<td>—</td>
</tr>
<tr>
<td>Kenya</td>
<td>258 763</td>
<td>85 392 33</td>
<td>23 000 (21 000–25 000)</td>
<td>1 256 (5.0–6.0)</td>
</tr>
<tr>
<td>Malawi</td>
<td>165 131</td>
<td>130 525 79</td>
<td>4 800 (4 400–5 200)</td>
<td>1 947 (37–45)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>292 083</td>
<td>130 420 45</td>
<td>17 000 (16 000–19 000)</td>
<td>—</td>
</tr>
<tr>
<td>Myanmar</td>
<td>33 415</td>
<td>33 61 10</td>
<td>16 000 (14 000–17 000)</td>
<td>553 (3.3–3.9)</td>
</tr>
<tr>
<td>Nigeria</td>
<td>202 434</td>
<td>40 855 20</td>
<td>39 000 (35 000–42 000)</td>
<td>6 254 (16–18)</td>
</tr>
<tr>
<td>Philippines</td>
<td>2970</td>
<td>1278 43</td>
<td>45 000 (41 000–49 000)</td>
<td>6 337 (13–16)</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>14 041</td>
<td>10 25 7.3</td>
<td>6 300 (5 700–6 800)</td>
<td>—</td>
</tr>
<tr>
<td>South Africa</td>
<td>1 091 549</td>
<td>409 496 38</td>
<td>49 000 (45 000–53 000)</td>
<td>—</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>—</td>
<td>—</td>
<td>19 000 (17 000–21 000)</td>
<td>1 314 (6.3–7.6)</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>—</td>
<td>—</td>
<td>16 000 (14 000–17 000)</td>
<td>1 774 (10–12)</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>125 740</td>
<td>38 489 31</td>
<td>7 600 (6 900–8 300)</td>
<td>2 333 (28–34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of people living with HIV (thousands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>2 215 755</td>
</tr>
<tr>
<td>Americas</td>
<td>66 598</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>4967</td>
</tr>
<tr>
<td>Europe</td>
<td>28 130</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>65 756</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>15 555</td>
</tr>
<tr>
<td>GLOBAL</td>
<td>2 396 761</td>
</tr>
</tbody>
</table>

— indicates data not available.

1 There were 22 other countries in the list of high TB or TB/HIV burden countries that did not report data for either risk group. These were Angola, Botswana, Brazil, Central African Republic, Chad, China, Congo, Democratic People’s Republic of Korea, Democratic Republic of the Congo, Ghana, Guinea-Bissau, India, Lesotho, Liberia, Namibia, Papua New Guinea, Russian Federation, Swaziland, Thailand, Uganda and Zambia.

2 In some countries due to data quality issues, the figures may not exclusively include number of people living with HIV who are newly enrolled in to HIV care.

3 Best estimates are followed by the uncertainty interval, and are shown to two significant figures.

**FIG. 5.2**

Provision of TB preventive treatment to people living with HIV, 2005–2015

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Global Tuberculosis Report 2016 :: 85
In April 2016, WHO in collaboration with the Republic of Korea’s Centers for Disease Control and Prevention, and International Tuberculosis Research Center organized a global consultation on the programmatic management of LTBI. This was the first such consultation in the era of the End TB Strategy, and brought together participants from both high and low TB burden countries to discuss and identify challenges, opportunities and best practices in the programmatic management of LTBI.

Barriers to monitoring and evaluation of the provision of treatment for LTBI that were identified included the non-notifiable status of LTBI in many countries, the existence of multiple paper-based registers for recording of treatment, fragmentation due to the involvement of multiple service providers and lack of regulation of the private sector.

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prevention and control policy, and TB and HIV programmes at national and subnational level should provide managerial direction to implement TB infection control measures. In health-care facilities and congregate settings, a comprehensive set of infection control measures – comprising administrative, environmental and personal protection measures – should be implemented.\(^1\) Periodic assessment of TB infection control in health-care facilities is essential to ensure that appropriate measures are in place.\(^2\)

In the latest revision of WHO guidance on monitoring and evaluation of collaborative TB/HIV activities,\(^3\) the risk of TB among health-care workers relative to the general adult population is an indicator recommended to measure the impact of TB infection control activities in health-care facilities. If effective TB infection control measures are in place, the relative risk of TB in health-care workers compared with the general adult population should be close to one.

In 2015, 9977 TB cases among health-care workers were reported from 67 countries; China accounted for 30% of these cases and South Africa for 21%. The notification rate among health-care workers could be calculated for 46 of the 67 countries; it ranged from zero in Belize, Gambia, Haiti, Jordan and Marshall Islands to 1565 cases per 100 000 population in South Africa. The notification rate among the general adult population in each country was calculated based on the number of notified TB cases in adults and the estimated size of the adult populations from the United Nations (UN) population division (2015 revision). The ratios of the TB notification rate among health-care workers to the rate in the general adult population are shown in Fig. 5.3. The ratio was above 2 in 16 countries, including South Africa. In the other four high TB/HIV burden countries for which the ratio could be calculated, the ratio was between 1 and 2 in three countries (Botswana, the Russian Federation and Zimbabwe) and below 1 in one country (China).

### 5.3 TB vaccination

There is a clear need for a vaccine that is more effective than BCG, especially to reduce the risk of infection with *Mycobacterium tuberculosis* and the risk of progression from infection to active TB disease in adults. Although there are 13 candidates in the TB vaccine pipeline, a new TB vaccine is not expected in the near future (Chapter 8).

BCG vaccination has been shown to prevent disseminated disease; this category includes TB meningitis and milia TB, which are associated with high mortality in infants and young children. Currently, WHO recommends that in countries with a high TB burden, a single dose of the BCG vaccine should be provided to all infants as soon as possible after birth, as part of childhood immunization programmes. In countries with low TB incidence rates, provision of BCG may be limited to neonates and infants in recognized high-risk groups, or to skin-test negative older children.

A summary of national policies on BCG vaccination\(^4\) is

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**FIG. 5.3**
Notification rate ratio of TB among healthcare workers compared with the general adult population, 2015

![Map showing notification rate ratio of TB among healthcare workers.](image)

**FIG. 5.4**
BCG vaccination policy by country

![Map showing BCG vaccination policy.](image)

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A. The country currently has a universal BCG vaccination programme.
B. The country used to recommend BCG vaccination for everyone, but currently does not.
C. The country never had universal BCG vaccination programmes.

The target population of BCG coverage varies depending on national policy, but is typically for the number of live births in the year of reporting.

shown in Fig. 5.4. Among 180 countries for which data were collected, 157 recommended universal BCG vaccination; the remaining countries had policies of selective vaccination for at-risk individuals in high-risk groups.

The latest data on BCG coverage (for 2015) are shown in Fig. 5.5. In the 163 countries that reported data, 102 reported coverage of above 90%. Among the 30 high TB burden countries, coverage ranged from 56% in the Central African Republic to 99% in Bangladesh, Brazil, Cambodia, China, Thailand and the United Republic of Tanzania. A further 16 of these countries reported coverage of at least 90%. Coverage was below 80% in seven of the high TB burden countries: Angola, Central African Republic, Kenya, Lesotho, Liberia, Nigeria and Papua New Guinea.

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1 [http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragebcg.html](http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tscoveragebcg.html)
Chapter 6 :: Universal health coverage, social protection and addressing social determinants: Implications for TB

**KEY FACTS AND MESSAGES**

Progress towards universal health coverage (UHC) is essential for all of the health-related Sustainable Development Goals (SDGs), including ending the tuberculosis (TB) epidemic. UHC is also closely aligned with the goal of ending poverty.

Two regularly monitored UHC financing indicators reveal the health financing conditions that must change in many of the highest TB burden countries to enable UHC and meet the ambitious milestones on route to end TB. These are total government spending on health as a proportion of gross domestic product (GDP) and out-of-pocket (OOP) expenditures as a share of total health expenditures. In 2014, government expenditures on health were less than the WHO benchmark of at least 6% in 150 of 191 countries (79%) for which data were available. OOP expenditures represented over 45% of overall health expenditures in 46 countries in 2014, including 11 of the 30 highest TB burden countries.

There are opportunities for improving TB service coverage as part of wider efforts, and examples are highlighted in this chapter, including:

- In some high TB burden settings, emerging UHC health financing schemes, including national health insurance, could lead to major reductions in OOP expenditures in low-income populations. Models need to explicitly include support for TB care and public health functions, and to address administrative and financing constraints that may otherwise hinder the impact of these schemes. More analysis is needed to inform their design and implementation but Thailand as well as countries in the Region of the Americas are good pathfinders.

- In Asia, building on established approaches to private provider engagement in TB care could help to address the burgeoning private sector in health-care delivery. This includes a combination of provider incentives and regulation, and application of innovative institutional intermediaries and communications technologies. Such levers can help to assure the quality of services provided.

- In the context of humanitarian emergencies and post-emergency system rebuilding, such as in the Eastern Mediterranean and sub-Saharan Africa, drug-supply coordination and cross-programme use of common laboratory technology are enabling access to TB and MDR-TB care and prevention.

- In Europe, modification of health system incentives is helping to improve patient-centred care, including by reducing costly hospitalization of patients with drug-susceptible TB and long stays for patients with MDR-TB, while expanding investments in outpatient care.

Social protection can be advanced through better models of care and social benefits. Many low- and middle-income countries have used international and community-level funds to finance social and economic support for TB and MDR-TB patients, but these support packages need to be better documented and evaluated. For overall impact and sustainability, using national social protection platforms is a priority.

The End TB Strategy includes a 2020 target to eliminate catastrophic costs for TB-affected households. WHO-recommended baseline national surveys are underway to assess the nature and severity of TB patient costs, and to improve service delivery and social protection accordingly. One country survey was conducted in 2015, eight began in 2016 and another ten are currently being planned for 2017–2018.

Ending TB and ending poverty are intertwined goals. Ministries of health, affected communities and partners can do more to use available evidence of the links in order to advocate for poverty elimination and action on related risk factors (e.g. noncommunicable disease prevention, food security, and housing).
This chapter aims to provide a tuberculosis (TB) perspective on what progress on universal health coverage (UHC) can mean for TB and for movement on other elements of the Sustainable Development Goal (SDG) agenda; for example, ending poverty, advancing social protection and reducing inequality.¹

It covers six topics:

- the definition and dimensions of UHC (Section 6.1);
- monitoring progress towards UHC (Section 6.2);
- opportunities for UHC and specifically for those affected by TB that are provided by innovations in financing and systems (Section 6.3);
- harnessing the benefits of social protection platforms (Section 6.4);
- assessing total costs borne by TB patients and the related occurrence of catastrophic total costs due to TB (Section 6.5); and
- linking with poverty elimination efforts and action on other social determinants of TB (Section 6.6).

This chapter is in large part descriptive. It addresses some of the challenges faced as countries embark on new UHC-related policies and schemes; it also discusses the health financing, social protection and social development opportunities that TB programmes and affected communities can build on in their efforts to end TB. Country experiences and epidemiological, policy and operational research inform the discussion.

6.1 Definition of universal health coverage

To achieve all of the health-related SDGs, WHO promotes the need for accelerated progress towards SDG Target 3.8 i.e. UHC by 2030 (see also Box 2.2 in Chapter 2). According to WHO and the World Bank, “UHC means all people receiving the health services they need, including health initiatives designed to promote better health, prevent illness, and to provide treatment, rehabilitation, and palliative care of sufficient quality to be effective, while at the same time ensuring that the use of these services does not expose the user to financial hardship”.²

UHC is a hugely ambitious aim and so far no country has fully achieved it; nevertheless, many countries have shown that dramatic gains are possible in low-, middle- and high-income settings. Furthermore, global health security depends on a commitment to UHC. As noted recently by Dr Margaret Chan, Director-General of WHO, “Well-functioning health systems that cover entire populations are now regarded as the first line of defence against the threat from emerging and re-emerging diseases”.³

Ending the global TB epidemic and resolving the multi-drug-resistant TB (MDR-TB) crisis depend on major movement towards UHC before 2025. There is no rationale for discussing universal coverage for interventions against one health challenge in isolation from the movement for UHC in general.

The dimensions of UHC efforts are reflected in the “UHC cube”, which is shown in Fig. 6.1, and examples are given of how each dimension is relevant for serving those affected by TB.

- The first dimension is expanding pooled funding to enable coverage of more of the population (including, for example, specific groups who are especially vulnerable to poverty, ill-health or rights barriers). In TB, this can mean ensuring that the poorest communities and marginalized groups (e.g. migrants, ethnic minorities) are covered by available social or national health insurance schemes and have better physical or legal access to services.
- The second dimension is expanding the services in any essential package covered by pooled funding. For TB, this may mean covering the costs of initial consultations, X-rays, second-line drugs, treating adverse events, and management of comorbidities and TB sequelae. All these services are essential for effective TB care.
- The third dimension is increasing the share of individual direct costs of care covered by pooled funds. Surveys of TB patient costs suggest that in many settings the financial burden is significant (on average equivalent to 50% of annual income), about half of which is incurred when using non-TB specific services in the public and/

or private sector, before TB diagnosis is made and TB treatment starts.¹

UHC efforts across all three dimensions could improve overall primary care service access and rapidly reduce the cost burden faced by patients.

### 6.2 Monitoring progress on universal health coverage

WHO and the World Bank have jointly proposed core indicators for monitoring progress towards UHC, addressing service access, health financing and financial protection.²

For measuring access, effective TB treatment coverage is among the proposed eight core service-access indicators that can be regularly monitored as “tracers” for overall UHC. Effective TB treatment coverage is defined as notifications, divided by incidence, multiplied by the treatment success rate.³

For health financing, UHC calls for the absolute level of funding for health care to be sufficient to ensure that it is possible to provide essential health services to the whole population. In addition, the costs of using those services, once available, must not be prohibitive (i.e. using them should not result in financial hardship). The three health financing indicators proposed for annual monitoring of progress towards UHC are:

- **Total government spending on health as a proportion of gross domestic product (GDP)** - the suggested benchmark is at least 6%⁴,⁵

- **Government health spending per capita in low-income countries** – the suggested benchmark in the Millennium Development Goal (MDG) era was US$86 (in 2012 prices).²⁴ A new benchmark for SDG-related health interventions for low and upper middle income countries will soon be recommended by WHO.

- **Out-of-pocket (OOP) expenditures as a proportion of total health expenditures** – the suggested benchmark is at most 15%.⁶ The level of OOP payments provides a proxy measure of the degree to which people lack financial protection.⁷

Country reporting against these three indicators is available in the WHO Global Health Expenditure Database.⁸

Two other indicators for assessing financial protection are proposed for periodic monitoring through population-based surveys:

- The proportion of households experiencing catastrophic health expenditures. This occurs when household OOP expenditures crowd out consumption of other necessary goods and services. Catastrophic health expenditures are defined as health-care expenditures that exceed a given fraction of the household’s expenditure. The fraction used by WHO and the World Bank is currently 25%.

- The proportion of people experiencing impoverishing expenditures, defined as the extent to which OOP expenditures push people into poverty, given a pre-defined “poverty line”. Accepted poverty lines vary. The international poverty line used by the World Bank uses the consumption indicator of US$1.50 or US$2.00 per day per capita at purchasing power parity. WHO uses a relative poverty line, based on a subsistence level of food expenditure.

Fig. 6.2, Fig. 6.3 and Fig. 6.4 provide an indication of where the 30 high TB burden countries stand in relation to three of the core health financing indicators described above.

**Total government spending on health as a proportion of GDP**

Fig. 6.2 shows the latest data (for 2014) on government health expenditures (GHE).⁹ GHE were less than 6% of GDP in most countries (150/191, 79%). In only 41 countries did GHE exceed 6% of GDP. Of these countries, only six are low or lower-middle income – Djibouti, Lesotho, Kiribati, Micronesia, Marshall Islands and Swaziland – and only one (Lesotho) is among the highest TB burden countries.

In 2014, government spending on health per capita was far below the suggested benchmark of US$86 per capita in all low-income countries (data not shown). Most countries spent less than US$20 per capita. The country that was closest to this benchmark was Senegal, which spent US$26 per capita.

In 2014, OOP expenditures were less than 15% of total health spending in 46 of the 190 countries for which data were available, including five of the 30 high TB burden countries: Mozambique, Namibia, Papua New Guinea, Thailand and South Africa (Fig. 6.3). There were 46 countries where OOP expenditures accounted for at least 45% of total health expenditures, including 11 high TB burden countries: Bangladesh, Cambodia, Central African Republic, India, Indonesia, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, Sierra Leone.

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⁵ This figure is determined by a combination of revenue generation and prioritization of health within government expenditures.


⁷ Note: OOP expenditures are defined as direct payments made to health-care providers by individuals at the time of health service use; therefore, they exclude prepayment.

⁸ http://apps.who.int/nha/database/Select/Indicators/en

⁹ WHO National health accounts database, accessed July 2016 via http://apps.who.int/nha/database
**FIG. 6.2**

Government spending on health, as a percentage of gross domestic product (GDP), 2014

**FIG. 6.3**

Out-of-pocket expenditures as a percentage of total health expenditures, 2014
Fig. 6.4 provides the breakdown of total health expenditures by source of funding, including OOP expenditures, for BRICS (Brazil, Russian Federation, India, China, South Africa) and other high TB burden countries, relative to the average breakdown for countries that are members of the Organisation for Economic Co-operation and Development (OECD). It suggests that most of the high TB burden countries have far to go in enabling substantial coverage of alternatives to OOP expenditures.

6.3 Innovations in domestic health financing and in health systems towards UHC

To dramatically reduce OOP expenditures and to more robustly fund health systems in general, mandatory pre-payment financing mechanisms (e.g. taxation, social or national health insurance schemes) need to form the core of domestic health financing. An estimate of the additional financing needed in low- and middle-income countries to move towards levels of health coverage in higher income countries is US$ 30 billion between now and 2035, with US$ 21 billion of this sum to be derived from increased domestic resources and US$ 9 million proposed to come from international sources. Box 6.1 provides a sense of how some pathfinding low- and middle-income countries in Asia are moving to develop more robust financing systems, and especially to address coverage for poor people. The national health insurance experience of Thailand, as well as experiences in a range of Latin American countries, provide good pathfinder examples of how to reach large shares of the population, including the poor, with health services free of catastrophic burden.

Beyond population-wide financing schemes, UHC means reaching those affected by TB, irrespective of where they seek care, including in the private sector. This requires a range of innovative demand- and supply-side approaches, as part of overall government stewardship of the health system as a whole. Box 6.2 provides an overview of some of the innovations being applied in Asia to harness the significant scope of the private sector while also enabling better quality of care overall. Countries in several regions have developed and applied mandatory case notification systems to engage with public and private institutions, and with providers not previously collaborating actively with national TB efforts. China’s well-established web-based communicable diseases notification system that incorporates TB has given a boost to TB case notifications from public hospitals. Similarly, NIKSHAY, India’s recent web-based, case-based TB notification system has led to a remarkable increase in case notifications from the private sector. In many countries of the Americas, high levels of case notification are possible through relatively strong public and social security sectors in health care.

To achieve UHC also requires enabling access for highly vulnerable populations. Target 1.5 of the SDGs is “by 2030, build the resilience of the poor and those in vulnerable situations and reduce their exposure and vulnerability to climate-related extreme events and other economic, social and environmental shocks and disasters”. In parts of the WHO Eastern Mediterranean Region, humanitarian emergencies brought on by civil unrest and war have led to large populations being internally displaced, and to a refugee crisis. Among the first steps towards regaining basic health service coverage, including TB care, has been securing adequate drug supplies and applying established good practices in screening, testing and care in emergencies. WHO and partners, including the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), the International

Note: mandatory pre-payment refers to pre-payments required for individuals either by the government, the employer and/or the individual themselves.


Innovative health financing schemes towards UHC, be they national health insurance (NHI) or other models, can potentially have profound and positive benefits for extending access to high quality health care to all those in need, including those affected by TB. This box provides some examples of the schemes and the main issues in assuring financing and coverage for TB and other services in selected high TB burden countries in Asia.

**Indonesia** is making strides towards UHC under its NHI programme or Jaminan Kesehatan Nasional (JKN), which was launched in 2014. The system is financed by premiums paid by employers, the employee and, for those with a low income, the national government. Beneficiaries can access a package of health services through public and selected private health-care providers, who are paid by capitation for primary health-care services and by reimbursement based on disease classification for hospital care. TB services covered include diagnosis and treatment services for drug-susceptible TB. In addition to the insurance scheme, there is also substantial budget-line support, including first-line TB drugs financed by the central government, and second-line drugs financed primarily by the Global Fund. High demand and costs, particularly in higher-level facilities, are challenging sustainability. Therefore, the government is in the process of reviewing the benefits package, including through cost-effectiveness analysis. The NTP is working with JKN, via Indonesia’s Centre for Health Financing and Health Security, to create TB service provision guidelines and monitoring tools for JKN. The government has announced its intention to shift financing of TB care and prevention to the NHI scheme, which is likely to lead to changes in access to TB medications and services. The mechanisms for financing public health functions are also in flux. A significant proportion of TB patients in Indonesia are treated in the private sector, and JKN may enable further leverage in promoting notification and quality care. By increasing investment in primary care, JKN may help to defray pre-TB diagnostic costs for patients.¹

**The Philippines** is committed to achieving UHC via investment in PhilHealth, the country’s NHI programme. The scheme is financed by government revenue and per capita premium payments, for which the government subsidizes the contribution for those identified by local governments as indigent. Local government units have a supplementary mechanism, whereby the units aggregate additional funds to finance local service delivery operations. TB services (hospitalization, first-line drugs, and consultations) are provided free of charge by PhilHealth to patients served by accredited providers. The programme is particularly important in encouraging private practitioners and institutions to provide standardized TB care. A series of operational challenges persist with PhilHealth. For example:

- not all patients are educated about the PhilHealth benefits or the locations of PhilHealth-accredited facilities;
- not all providers are in the PhilHealth system due to the complex accreditation system;
- reimbursement processes can impede interest of providers to pursue the accreditation process; and
- currently, MDR-TB is not included in the benefits package but an expansion of the programme is being formulated.

Under the updated National Strategic Plan for the NTP, measures are proposed to resolve several of these bottlenecks.²

**Viet Nam** is expanding its social health insurance (SHI) system with the aim of achieving universal coverage by 2020. The scheme is financed by a combination of national revenue and employer–employee contributions. The government tax revenue subsidizes the premium for the poor and for ethnic minorities, with partial subsidies for the near-poor and students. Since May 2016, under the SHI, latent TB infection, TB diagnosis and treatment services are covered by the government, although users contribute a co-payment that ranges from 0% to 20%. The NTP has plans to establish a foundation that can cover co-payment of TB patients and the premium for TB patients who do not yet have a health insurance card. One area of concern is drug supply, which will shift under SHI financing. Currently, first-line TB drugs have been financed and distributed by the central government, and second-line TB drugs by the Global Fund. The NTP is now working with counterparts within the Ministry of Health and the SHI agency to ensure that financing is secure from central SHI resources, to maintain a full supply of quality-assured drugs to TB patients.³

**Thailand** has a robust and progressive NHI scheme in place. There are three schemes for Thai nationals: the Universal Coverage Scheme (UCS), the Social Security Scheme and the Civil Servants Medical Benefit Scheme. These schemes cover 99% of the Thai population. In 2013, the Ministry of Public Health initiated a scheme for migrants not covered under the social security scheme and, by the end of 2015, nearly 1.45 million migrants could purchase subsidized health insurance. The UCS currently covers about 75% of the Thai population. It is entirely tax-revenue financed, and is administered by the National Health Security Office (NHSO), an independent government agency that purchases and reimburses services. The Ministry of Public Health provides the quality standards, public health functions and consolidation of case reporting. Financing for TB services is channelled through the TB Fund within the NHSO. UCS provides free first-line and second-line TB and MDR-TB treatment, molecular diagnostics for certain groups and resistance monitoring. Overall, coverage for TB services appears to be high, with additional UHC efforts under way to cover previously uncovered populations, such as migrants – an important risk group for TB. The NHSO and NTP are in the process of addressing gaps and discrepancies in TB information flow by harmonizing systems. Improved information will enable further review of the quality of TB care provided.⁴

Continued
Enabling or expanding financing for MDR-TB treatment is among the ongoing challenges under all of the evolving schemes above.¹


Box 6.1 continued

China has NHI schemes that are estimated to reach 95% of the population. The Basic Medical Insurance scheme is co-financed by government revenue and per capita premium payments. Under recent health-care reforms, China is moving towards a mixed source funding mechanism, whereby funds from multiple levels of government, individual beneficiaries and social assistance programmes will be pooled to improve financial sustainability. At the same time, reforms have altered the delivery model for TB care. Patients will no longer access care from TB dispensaries, and state-owned hospitals will be the primary TB service providers. Basic TB care in these hospitals is technically free, but a complicated reimbursement mechanism combined with benefit package limitations may result in high costs for drug-sensitive TB services.²

Enabling or expanding financing for MDR-TB treatment is among the ongoing challenges under all of the evolving schemes above.¹


In middle-income countries, UHC progress and better disease control often depend on reforming well-established health system institutions, management and financing mechanisms. Box 6.4 offers an example of the ramifications of health financing approaches, specifically in Central and Eastern Europe, for patient care and cost burdens overall. It also highlights efforts underway through research, policy dialogue and collaboration to overcome the bottlenecks.

6.4 Harnessing the benefits available with social protection platforms

As has been well documented, and advocated for in the SDGs and the End TB Strategy, social protection can contribute to ending poverty and ending disease epidemics, including those of TB and HIV. Action for UHC is in itself a major lever for social protection. Ecological studies suggests that there is an inverse association between government investment in social protection and national TB incidence in countries worldwide.³

There are varying institutional definitions of social protection, but the broad concepts are clear. Social protection represents a system of policies and programmes that seek to reduce poverty and support


:: Box 6.2
Innovations in engaging private care providers in Asia

For a large proportion of people with TB in Asia, the pathway to care begins with a visit to a neighbourhood private practitioner. In scaling up engagement of all care providers through public-private mix (PPM) approaches, working with numerous formal and informal, weakly organized and poorly regulated private practitioners is both demanding and resource intensive for NTPs (see Table 4.2 in Chapter 4). Intermediary organizations in high TB-incidence countries in Asia have worked with NTPs to address collaboration with private practitioners by developing and implementing innovative models of engagement. The results are impressive; some have been published and some presented in a recent meeting of the global PPM Working Group. In the social franchising model in Myanmar, which was designed, implemented and scaled up with the assistance of an international NGO, franchisee practitioners use integrated service delivery to contribute 15% of all TB cases notified in the country while also achieving high treatment success rates that are comparable to those reported by public sector health centres (see Box 4.2). Social franchising for TB care provision has been as successful in other settings as it is for reproductive health and other public health programmes.

Breaking away from the traditional methods, the social business models developed and implemented by another international NGO in Bangladesh and Pakistan incorporate active screening for TB in private clinics, private hospitals and laboratories, while also providing access to new rapid diagnostic tests at subsidized or no cost for TB patients in private clinics. TB screening in private clinics in the megalopolis of Karachi doubled the case notifications from the city in a year; also, over 2000 additional TB cases were detected by public–private mix (PPM) approaches, working with numerous formal and informal, weakly organized and poorly regulated private practitioners is both demanding and resource intensive for NTPs (see Table 4.2 in Chapter 4). Intermediary organizations in high TB-incidence countries in Asia have worked with NTPs to address collaboration with private practitioners by developing and implementing innovative models of engagement. The results are impressive; some have been published and some presented in a recent meeting of the global PPM Working Group. In the social franchising model in Myanmar, which was designed, implemented and scaled up with the assistance of an international NGO, franchisee practitioners use integrated service delivery to contribute 15% of all TB cases notified in the country while also achieving high treatment success rates that are comparable to those reported by public sector health centres (see Box 4.2). Social franchising for TB care provision has been as successful in other settings as it is for reproductive health and other public health programmes.

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Use of digital tools has helped significantly in facilitating project operations and in ensuring adherence to recommended routines by both providers and patients in private clinics.

“Private provider interface agency” models are being implemented by an international NGO in close collaboration with the NTP and the local TB programmes in three cities in India (Mehsana, Mumbai and Patna). These models have produced impressive results with a remarkably large yield of TB cases: nearly 2000 additional TB cases every month in Mumbai alone. The package of innovations that suits the ecosystems of private health care in the respective cities includes introduction of vouchers for free diagnosis and free drugs for patients in private clinics through linkages with private laboratories and pharmacies in the neighbourhoods, and tiered referrals to access these services. The projects ensure that all the essential tasks required to ensure quality TB care provision are accomplished through smart use of digital tools and technologies such as a call centre, mobile phones, electronic notifications and short text messages.

Another pioneering and innovative initiative in India has successfully fostered a partnership between private laboratories and manufacturers to support adoption of a low-price, high-volume model that improves access to new diagnostics and strengthens linkages between public and private sectors.

:: FIG. B6.2.1
Innovations in TB public-private mix (PPM) models

<table>
<thead>
<tr>
<th>Collaboration (Enablers and incentives)</th>
<th>Laws and regulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoH/NTP Stewardship</td>
<td>Intermediary (Public, NGO, Private)</td>
</tr>
<tr>
<td>Access to (free) drugs and diagnostics</td>
<td>Digital tools for ease of operations</td>
</tr>
<tr>
<td>PP</td>
<td>PH</td>
</tr>
<tr>
<td>NGO</td>
<td>Community/People with TB</td>
</tr>
</tbody>
</table>

MoH: ministry of health; NTP: national tuberculosis programme; NGO: nongovernmental organization; PH: public hospital or private hospital; PP: private provider (formal, informal, pharmacy, laboratory)
In 2015, some 29,809 TB cases were reported in the three post-Ebola West African countries: Guinea, Liberia, and Sierra Leone. WHO estimates that Liberia and Sierra Leone are among the 10 countries with the highest TB rates per capita worldwide. Reported cases for the three countries represent only 42–60% of the estimated incident TB cases, and population-based surveys are needed to improve estimates. With financing from the United States Agency for International Development (USAID) and from the Global Fund, WHO is supporting the strengthening of TB capacity accompanying other efforts to strengthen health systems.

During the Ebola outbreak, Guinea, Liberia, and Sierra Leone all received support from partner agencies to introduce GeneXpert instruments for Ebola screening. As these countries transition from the outbreak response to routine disease surveillance, an opportunity has arisen for the integration of these instruments into the general laboratory network, including for testing for TB, rifampicin-resistant TB and HIV viral load. A review of the current placement of the machines will inform the best deployment to serve the multiple needs of the populations covered. The assessment is taking into consideration epidemiology, availability of other companion diagnostic tools, laboratory personnel and power supply. In all three countries, WHO is supporting the data managers of the TB programmes to map TB cases notified by prefecture or district, and to calculate needs for the rapid molecular diagnostic tool based on recommended diagnostic algorithms. The Foundation for Innovative New Diagnostics (FIND), a non-profit public–private partnership that helps to enable evidence generation and roll-out of new diagnostic tools, is providing training using the Global Laboratory Initiative-endorsed Xpert MTB/RIF training package.

Other health systems platforms that emerged in response to the Ebola outbreak can also improve timely TB diagnosis. For example, in 2015, the Ministry of Health and Social Welfare of Liberia invited Riders for Health (RFH), an NGO, to manage their fleet of 250 new vehicles and 200 new motorcycles donated during the Ebola outbreak. RFH offers transportation of medical samples to the nearest laboratory for testing. Planning is underway, with NTP and Global Fund financing, to enable transfer of sputum samples from anywhere in the country to Xpert MTB/RIF sites and the central TB laboratory.

1 42% estimated case detection coverage in Liberia, 55% in Guinea and 60% in Sierra Leone.
MDR-TB poses a particular challenge in WHO’s European Region, which has nine of the world’s 30 high MDR-TB burden countries. For both patient-centered care and cost-effectiveness, TB care is best delivered in the community. Nevertheless, many of these high MDR-TB-burden countries still provide substantial inpatient care for patients with drug-susceptible and drug-resistant TB (see Fig. B6.4.1 and Fig. B6.4.2). Some historical systems of institutional staffing, payment and reimbursement created perverse incentives in many settings to hospitalize patients unnecessarily, or for much longer periods than required. These incentives often persist. Also, for lack of resources (and insufficient capacity), outpatient and primary care services have been ill-prepared to provide adequate TB and MDR-TB treatment and care. Major challenges to enable greater outpatient care include developing appropriate, country-specific TB care delivery models; creating sustainable financing mechanisms for TB care; ensuring adequate human resources; and providing social protection for TB patients. With technical support, many of these countries are increasing their efforts to reduce hospitalization rates by improving patient-centred outpatient services, decreasing the number of TB beds and the unnecessarily long duration of hospital stays, reallocating TB budgets accordingly, and reassigning staff in hospitals to overall pulmonary and primary health care.

In a concerted effort to support countries to face their MDR-TB challenge and the necessary reform of systems, the Center for Health Policies and Studies (PAS) and the WHO Regional Office for Europe (EURO) conceived the Tuberculosis Regional Eastern European and Central Asian Project (TB-REP), which is funded by the Global Fund. The aim of TB-REP is to use a systems-based approach to improve TB treatment outcomes and accelerate progress in ending the epidemic by removing health system barriers and scaling up health system reforms. The project complements country TB-specific and broader health reform efforts supported by...
To document costs and identify the main cost drivers to—

3 To determine the association between costs and treatment outcome (using routine cohort data).

A key indicator that can be derived from a survey is the proportion of patients with catastrophic total costs due to TB. This is defined for operational purposes as the number of TB patients (and their households) who experience catastrophic total costs divided by the number of all TB patients treated in the NTP network. Catastrophic total costs is defined as total costs (indirect and direct combined) incurred during illness and treatment that exceed a given threshold (e.g. 20%) of the household’s annual income. The numerator is the total direct and indirect costs incurred from the onset of symptoms to the end of TB treatment for the household, and the denominator is annual household income.

This TB-specific indicator of catastrophic total costs is distinct from the indicator that WHO uses to measure financial protection. WHO uses the share of the population incurring “catastrophic expenditures”, which, as noted above, refers to OOP expenditures for health care (for all


<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>INTERVENTIONS</th>
<th>CHALLENGES</th>
<th>MEASURES TAKEN TO IMPROVE EFFECTIVENESS</th>
<th>SOCIAL PROTECTION PLATFORMS</th>
</tr>
</thead>
</table>
| Belarus     | In-kind food, transport and cash support to MDR-TB patients                                                                                                                                                                                                                                                                                  | Large MDR-TB patient population, many of whom have other social service needs (e.g., related to alcohol and drug use)                                                                                     | • Increased domestic budget for social support enables donor support transition  
  • Linkage with NHI  
  • Direct bank cash transfers and in-kind support  
  • Transportation support for prisoner release liaison                                                                 | Large scale:  
  • NHI, sick leave and disability coverage, social services                                                                                                                                  |
| Brazil      | Food parcels and some discrete cash and transport support; targeted efforts for vulnerable groups                                                                                                                                                                                                                                            | Resource constraints inhibit expansion; slow process to link formally with cash-transfer system                                                                                                             | • NTP has prioritized the challenge  
  • Documented link of improved TB treatment outcomes with cash transfers  
  • Further research is under way  
  • Institutional and parliamentary discussions on linking TB patients with cash-transfer programme                                                                 | Large scale:  
  • Bolsa Familia – cash transfer programme for women and children  
  • Linkages with health services and education                                                                                                                                             |
| India       | Range of interventions from food and vouchers, small facility payments to patients, social welfare payment access, prepayment cards, etc.                                                                                                                                                                                                         | Limited patient coverage, wide variability across states and localities on TB-specific support packages, and weaknesses in administration; NGOs play a role but not formally linked | • Stated concern of government  
  • Operational research studies documenting inputs and results  
  • Sharing of state-specific experiences in TB patient cash transfers, nutrition and social service linkages  
  • NGO engagement to help patients access benefits  
  • Efforts to link online TB register to the national unique identifier system used for other major social programmes                                                                 | Large scale:  
  • Food support, including:  
    — Antyodaya Anna Yojana  
    — Food Security Act  
  • Financial support: state-level and national-level initiatives  
  • Disability and livelihood schemes                                                                                                                                                    |
| Kenya       | Food packages, targeting undernourished MDR-TB patients; food support and some cash transfers; transport                                                                                                                                                                                                                                   | Financing limits extension and level of patient support                                                                                                                                                   | • NTP priority  
  • Assessment of nutritional status of patient cohorts, nutritional needs and district TB performance review  
  • Linkage to national nutrition programme and external donors for more coverage of MDR-TB patients  
  • Active link with national insurance subsidy programme                                                                                                                         | Large scale:  
  • Vision 2030 – national development agenda  
  • National social development policy and health sector services fund  
  • National insurance subsidy programme  
  • National nutrition programme                                                                                                                                                    |
| Myanmar     | Food packages and/or cash transfers for MDR-TB patients from major project financing; additional NGO and community contributions                                                                                                                                                                                                       | Different sources funding different levels of food support, even within single health facilities; financing limits coverage                                                                             | • Supportive donor community  
  • NTP-led effort for standardization of food package levels and cash transfers for MDR-TB patients  
  • Social protection included in new National TB Strategic Plan                                                                                            | • National social protection strategy and programme under development  
  • UHC-oriented health policies including essential package of free services and service extension                                                                              |
| Philippines | Food and transport support, especially for MDR-TB patients, and piloting of conditional cash transfer                                                                                                                                                                                                                                     | Financing limits coverage and administrative bottlenecks, with variability in practice                                                                                                                     | • Patient support advocated for in new legislation  
  • Donor support for related operational research  
  • Active system for inclusion of patients with PhiHealth, and outreach to conditional cash-transfer programme                                                                 | Large scale:  
  • Bridging Program for the Filipino Family conditional cash transfer (4Ps)  
  • Listahan – register of families living in poverty  
  • PhiHealth – NHI programme                                                                                                                                                    |
| South Africa | Food packages, or vouchers, and transport support for MDR-TB patients, other NGO and local area provided benefits; some disability grant and other grant recipients                                                                                                                                                                 | Widely variable support elements for TB or MDR-TB patients in different states and facilities; variable application of disability grant access for hospitalized and needy ambulatory patients | • New collaboration across health, social development and benefits administration agency  
  • Research and patient costing efforts  
  • Enhancement of information on disability grants and other grants; strong opportunities for engagement with community organizations, and to expand TB linkages to range of social development  
  • Additional domestic TB financing mobilized                                                                                                                                               | Large scale:  
  • Child Support grant  
  • Care Dependency grant  
  • Disability grant  
  • Social Relief of Distress grant  
  • Workmen’s Compensation Fund  
  • NHI in process                                                                                                                                       |
| Various low-income countries – nutrition focus | Food packages, vouchers or cash provided by the WFP, often with financing from The Global Fund and sometimes linked as part of HIV-targeted food assistance                                                                                                                                                                                                 | Variability in defining beneficiaries and in documentation; financial constraints and sustainability issues                                               | Potential for:  
  • improved use of WHO nutrition and TB care guidance  
  • improved assessment to determine beneficiaries, and  
  • increased monitoring and evaluation, and engagement with national food or nutrition partners                                                                                     | National nutrition programmes vary in coverage – small scale in many low-income settings, except where supported by WFP, relief agencies, NGOs                                                      |

The Global Fund, The Global Fund to Fight AIDS, Tuberculosis and Malaria; HIV, human immunodeficiency virus; MDR, multidrug resistant; NGO, nongovernmental organization; NHI, national health insurance; NTP, national TB programme; TB, tuberculosis; UHC, universal health coverage; WHO, World Health Organization; WFP, World Food Programme.

Sources: Operational documents of NTPs, Ministries of Health and social welfare and development ministries, The Global Fund, World Food Programme.
conditions) exceeding a given fraction of a household’s total consumption. The “catastrophic expenditures” indicator focuses on the financial burden that households face from the payments that they make for health services for any of their members, and general household surveys are used to generate the data on all health-care spending and to compare OOP expenditures to overall household consumption. The “catastrophic total costs due to TB” indicator, on the other hand, is based on data from interviews with TB patients in health facilities. It captures the total economic burden, including payments for care (e.g. diagnostic and treatment services, and medicines), payments associated with care seeking (e.g. travel costs) and the “opportunity costs” associated with care seeking (e.g. lost income).

For these reasons, the TB-specific measures of “catastrophic total costs due to TB” are not comparable with the population-based “catastrophic expenditures” measure of financial protection referred to in Section 6.2. However, the TB-specific estimates of these costs are relevant to UHC because they offer the potential to provide useful information on the magnitude and nature of demand-side barriers to access care (take-up and completion), and can make an important contribution to the diagnosis of barriers to progress towards UHC.

Fig. 6.5 provides an overview of the status of planning and conduct of TB patient cost surveys following WHO recommendations. Box 6.5 presents a summary of findings from a survey conducted in Myanmar.

6.6 Ending poverty and addressing other social determinants of TB

As shown in Fig. 6.6, there is a strong inverse association between GDP per capita and TB incidence.

The first goal of the SDGs is ending poverty in all its forms everywhere and it includes two targets for 2030. The first (Target 1.1) is to eradicate extreme poverty for all people everywhere, currently measured as people living on less than US$ 1.25 a day. The second (Target 1.2) is to reduce at least by half the proportion of men, women and children of all ages living in poverty in all its dimensions, according to national definitions.

Societies that have experienced broad socioeconomic development have seen a substantial reduction in TB incidence and mortality rates. Poverty alleviation has historically contributed the most to the reduction in TB rates in countries that now have a low TB burden. However, economic growth alone is not a guarantee for a rapid decline in TB cases and deaths. Unequal wealth distribution, with large parts of the population are left behind, leaves fertile ground for a sustained TB burden.

Not all economic development is of benefit to the fight against TB. Industrialization with rapid urbanization increases population density and is often coupled with rapid growth of urban deprivation and overcrowded slums. Dramatic lifestyle changes in emerging economies – for example, increasing smoking and alcohol use, and changes in diet and exercise – can have a negative impact on TB rates via an increase in noncommunicable diseases that act as risk factors for TB. In most societies, the poorest are also the worst affected by these risk factors and diseases. Underfunded or poorly organized health systems are often not equipped to ensure equitable access to high-quality TB diagnosis and treatment. The poorest and most vulnerable groups face severe barriers to accessing diagnosis and treatment, and to staying in care. They also have a particularly high risk of suffering severe financial and social consequences as a result of TB, and may have the least access to any social protection mechanisms. Although poverty is a cause of TB, the disease is also a cause of poverty; this vicious circle plays out on individual, household and community level.

There is strong evidence of major direct social, medical and behavioural risk factors for TB, many of which are also closely linked to underlying poverty. Table 6.2 provides a summary review of the population attributable fraction (PAF) for some TB risk factors with large population-level impact. The PAF is an estimate of the relative reduction in TB incidence that would result from the elimination of a given risk factor. PAF estimates can be used to more effectively advocate for the reduction of these risk factors, through public health interventions and efforts to address their underlying social determinants.

The table includes only a few of the known TB risk factors, focusing mainly on risk factors for progression from TB infection to active disease. The table does not include some important risk factors such as contact with people with infectious TB, crowding, poor ventilation and silicosis. Moreover, the calculation of the PAF does not consider the secondary effects of TB transmission from people that fall ill with TB. In addition, due to a lack of detailed global data on the distribution of the various risk factors in the population, the estimations assume the same prevalence of the risk factors in all (adult) population segments. More sophisticated estimations can be made when risk factor distribution data are available, and when the dynamic effects of indirect prevention of onward transmission are modelled. Such models are conceptually more appropriate, but they also introduce more uncertainty into the estimated impact of changes in risk factor exposure. Box 6.6 provides an introduction to some ongoing modelling efforts to assess the effect of measures to reduce risk factors on future TB burden in selected countries.

In response to social determinants of TB, there are a number of societal-level actions that can help to drive effective TB prevention beyond the poverty alleviation, UHC financing and social protection discussed above, for which governments are ultimately responsible. Societal-level actions include:

- integrated public health programmes that help to reduce diabetes, smoking and harmful alcohol use;
**Box 6.5**

**Myanmar TB patient cost survey**

In Myanmar, from December 2015 to February 2016, the Ministry of Health worked with a national research partner to conduct a nationally representative patient cost survey involving 996 eligible TB patients in health facilities. Myanmar is a low-income country with among the highest TB burdens in the WHO South-East Asia Region. The survey was the first to apply the new WHO-recommended protocol for TB patient cost surveys and to adapt its instrument. The cross-sectional survey included questions on the patient’s current treatment and retrospective questions on the costs incurred by patients for this illness episode before they were diagnosed as having TB. Current costs were extrapolated for the full treatment duration to estimate total costs (both direct and indirect) for the whole TB episode, as a percentage of household income. If total costs exceeded 20% of annual household income, the TB-affected household was deemed to have faced catastrophic costs.

The survey results suggested that, in Myanmar, an estimated 65% of TB-affected households face catastrophic costs. On average, total TB-related costs were US$1178 per household and the largest proportion of this total was accounted for by foregone income (49%) followed by nutritional supplement costs (25%), and post-diagnosis medical costs (14%). Being on MDR-TB treatment and in a lower household wealth quintile were both significant predictors of facing catastrophic costs.

The high proportion of TB-affected households experiencing catastrophic costs bolsters the need for effective, patient-centred health care free of charge, and the need for social protection. The large proportion of total spending attributable to lost wages and food or nutritional supplements suggests that efforts to reduce income loss (reduced time spent seeking care through decentralization and more patient-friendly service organization, as well as employment protection), income support and/or food support may need to be considered to reduce the burdensome costs faced by patients and their families. The NTP is convening a consultation to review the results, and to further discuss the probable dynamics behind the highest areas of spending and the income losses associated with TB and its treatment. The participants will consider the probable policy and practice implications, and further operational research that might be needed. The results should inform ongoing work on Myanmar’s first national social protection strategy, and its ongoing efforts to strengthen health services.
Population attributable fractions for risk factors for TB

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>Prevalence (%)</th>
<th>Population Attributable Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>21</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Undernutrition</td>
<td>3.2</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.1</td>
<td>8.5</td>
<td>15</td>
</tr>
<tr>
<td>Alcohol misuse</td>
<td>2.9</td>
<td>4.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.9</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>Indoor air pollution</td>
<td>1.4</td>
<td>53</td>
<td>17</td>
</tr>
</tbody>
</table>


Estimate of prevalence is based on a weighted average (by population size) for the 30 high TB burden countries.

In moving forward to end TB and on the SDGs in general, there needs to be close collaboration across and beyond government on multiple development priorities. Hence, this global TB report includes results for some key SDG indicators for the 30 highest TB burden countries (Table 6.3). As the colour coding in the table shows, most of the highest TB burden countries have indicators suggesting lower than average status relative to benchmarks. Therefore, there is a substantial challenge ahead to ramp up investment and commitment to the new development agenda.

- Food security initiatives for high-risk populations and regions;
- Environmental protection, especially in certain industries (e.g. mining);
- Building codes (e.g. for homes, workplaces, health facilities, prisons, schools and institutions for elderly) that are conducive to infection control;
- Good urban planning (e.g. with slum upgrading); and
- Effective and safe energy and cooking devices that minimize pollution.
## TABLE 6.3
Status of selected SDG indicators in August 2016, 30 high TB burden countries

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>SDG 1 INDICATOR</th>
<th>SDG 2 INDICATOR</th>
<th>SDG 10 INDICATOR</th>
<th>SDG 11 INDICATOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PROPORTION LIVING ON LESS THAN US$1.25 (PPP) PER DAY</td>
<td>PROPORTION OF POPULATION UNDERNOURISHED</td>
<td>GINI COEFFICIENT (%)</td>
<td>PROPORTION OF URBAN POPULATIONS LIVING IN SLUMS</td>
</tr>
<tr>
<td>Angola</td>
<td>43</td>
<td>14</td>
<td>43</td>
<td>56</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>43</td>
<td>16</td>
<td>32</td>
<td>55</td>
</tr>
<tr>
<td>Brazil</td>
<td>3.8</td>
<td>5.0</td>
<td>53</td>
<td>22</td>
</tr>
<tr>
<td>Cambodia</td>
<td>10</td>
<td>14</td>
<td>31</td>
<td>55</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>63</td>
<td>48</td>
<td>56</td>
<td>93</td>
</tr>
<tr>
<td>China</td>
<td>6.3</td>
<td>9.3</td>
<td>42</td>
<td>25</td>
</tr>
<tr>
<td>Congo</td>
<td>33</td>
<td>31</td>
<td>40</td>
<td>47</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>—</td>
<td>42</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>DR Congo</td>
<td>88</td>
<td>—</td>
<td>42</td>
<td>75</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>37</td>
<td>32</td>
<td>33</td>
<td>74</td>
</tr>
<tr>
<td>India</td>
<td>24</td>
<td>15</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Indonesia</td>
<td>16</td>
<td>7.6</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>Kenya</td>
<td>43</td>
<td>21</td>
<td>—</td>
<td>56</td>
</tr>
<tr>
<td>Lesotho</td>
<td>56</td>
<td>11</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>Liberia</td>
<td>84</td>
<td>32</td>
<td>37</td>
<td>66</td>
</tr>
<tr>
<td>Mozambique</td>
<td>61</td>
<td>25</td>
<td>46</td>
<td>80</td>
</tr>
<tr>
<td>Myanmar</td>
<td>—</td>
<td>14</td>
<td>—</td>
<td>41</td>
</tr>
<tr>
<td>Namibia</td>
<td>24</td>
<td>42</td>
<td>61</td>
<td>33</td>
</tr>
<tr>
<td>Nigeria</td>
<td>62</td>
<td>7.0</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>Pakistan</td>
<td>13</td>
<td>22</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>Papua New Guinea</td>
<td>36</td>
<td>—</td>
<td>44</td>
<td>—</td>
</tr>
<tr>
<td>Philippines</td>
<td>19</td>
<td>14</td>
<td>45</td>
<td>38</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>0</td>
<td>—</td>
<td>27</td>
<td>—</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>57</td>
<td>22</td>
<td>34</td>
<td>76</td>
</tr>
<tr>
<td>South Africa</td>
<td>9.4</td>
<td>5.0</td>
<td>63</td>
<td>23</td>
</tr>
<tr>
<td>Thailand</td>
<td>0.3</td>
<td>7.4</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>UR Tanzania</td>
<td>44</td>
<td>32</td>
<td>38</td>
<td>51</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>2.4</td>
<td>11</td>
<td>39</td>
<td>27</td>
</tr>
<tr>
<td>Zambia</td>
<td>74</td>
<td>48</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>—</td>
<td>33</td>
<td>—</td>
<td>25</td>
</tr>
<tr>
<td><strong>High-burden country average</strong></td>
<td><strong>35</strong></td>
<td><strong>22</strong></td>
<td><strong>42</strong></td>
<td><strong>48</strong></td>
</tr>
<tr>
<td><strong>Global average</strong></td>
<td><strong>18</strong></td>
<td><strong>11</strong></td>
<td><strong>36</strong></td>
<td><strong>33</strong></td>
</tr>
</tbody>
</table>

— Indicates values that were not available. PPP, purchasing power parity.

* Data come from the United Nations Statistics Division SDG indicator database. Individual data points are coloured pink if they are worse than the global average and green if better than the global average.

* The Gini coefficient is a measure of statistical dispersion intended to represent the income distribution of a country’s population and is the most commonly used measure of inequality. Generally, the coefficient ranges from 0% to 100%; a value of 0% expresses complete equality between everyone in the population, and a value of 100% expresses maximum inequality in the population i.e. one person has all the income.
To quantify the population-level impact of a risk factor on the burden of TB, previous studies have reported the population attributable fraction (PAF) for one specific risk factor. The PAF incorporates information on the prevalence of risk factor exposure and the strength of association (often measured as relative risks) between the risk factor and TB disease. Relatively straightforward to calculate, PAF can be interpreted as “the proportion of TB burden that would be prevented if the risk factor exposure were removed, with other things the same”. Despite its popularity, the PAF approach has two limitations. First, it assumes that the probability of disease is independent among individuals, which is clearly not the case for TB. In other words, the approach does not account for the impact of a risk factor on disease transmission and therefore often understimates the overall population-level impact. Second, the PAF approach is “timeless” and cannot be used to project the impact of risk factor reduction on the future trend of TB epidemiology.

A few studies have applied dynamic modelling of TB transmission to investigate the impact of risk factors on TB. Dynamic models incorporate the natural history of TB (susceptible or latent infection, active disease or recovered) and the effect (relative risk) of risk factors on the natural history of TB (e.g. increasing the rate of reactivation or increasing the case fatality rate upon having disease). This type of model accounts for the transmissible nature of TB disease and can be used for the purpose of future projections, although caution is needed when interpreting the results from such complex models. To illustrate, two examples of such dynamic modelling are provided below.

- In a dynamic modelling study conducted in China, Lin et al. projected the potential impact of reducing tobacco smoking and indoor air pollution from solid fuels on the trend of TB incidence. The study found that aggressive interventions on smoking and indoor air pollution could accelerate the decline of TB incidence (Fig. B6.6.1).

- Pan et al. investigated the impact of diabetes prevention on TB morbidity and mortality in 13 high burden countries without a generalized HIV epidemic (Afghanistan, Bangladesh, Brazil, Cambodia, China, India, Indonesia, Myanmar, Pakistan, Philippines, Russian Federation, Thailand and Viet Nam). These countries cover over 60% of all incident TB cases globally. The study indicated that, in the worst case scenario in which diabetes prevalence increases greatly over the next two decades, the TB incidence would increase (reversing the current slow rate of decline in TB incidence). On the other hand, simply stopping the rise in the prevalence of diabetes would accelerate the decline of TB, preventing 6.0 million TB cases and 1.1 million TB deaths in the 13 countries over 20 years. Aggressive interventions that reduce diabetes incidence would have an even larger impact on TB, avoiding 7.8 million cases and 1.5 million deaths. See Fig. B6.6.2.


Projected TB incidence/mortality/prevalence (B/C/D) under different scenarios of diabetes control (A) in 13 high TB burden countries, 2015–2035

Chapter 7 :: TB financing

KEY FACTS AND MESSAGES

The Stop TB Partnership’s Global Plan to End TB, 2016–2020 estimates that in low- and middle-income countries US$ 52 billion is required over 5 years to implement interventions that are currently available. The amount required will increase from US$ 8.3 billion in 2016 to US$ 12.3 billion in 2020. Most of this funding is for drug-susceptible tuberculosis (TB) (e.g. US$ 6.4 billion in 2016), but the amount for multidrug-resistant TB (MDR-TB) doubles from US$ 1.7 billion in 2016 to US$ 3.6 billion by 2020; the remainder is for TB/HIV interventions. Over the period 2016–2020, a further US$ 6 billion is needed for high-income countries, and an additional US$ 9 billion is needed for TB research and development.

Based on data reported to WHO by 126 countries with 97% of the world’s notified TB cases, US$ 6.6 billion was available for TB prevention, diagnosis and treatment in low- and middle-income countries in 2016. This is an increase from previous years, but is still about US$ 2 billion less than the estimated requirement for this group of countries in the Global Plan. Increased domestic and international donor commitments are needed to close the funding gaps.

Of the US$ 6.6 billion available in 2016, 84% was from domestic sources. However, this aggregate figure is strongly influenced by the BRICS countries (Brazil, the Russian Federation, India, China and South Africa), which collectively account for about 50% of the world’s TB cases, and rely mostly or exclusively (the exception is India) on domestic funding. In other countries with a high TB burden, international donor funding dominates, accounting for 75% of reported funding in the group of 25 high TB burden countries outside BRICS, 87% of funding in low-income countries and 60% of funding in lower middle-income countries. The single largest source of international donor funding is the Global Fund to Fight AIDS, Tuberculosis and Malaria.

International donor funding for TB falls far short of donor contributions for HIV and malaria. The latest data from the Organisation for Economic Co-operation and Development (OECD) creditor reporting system show totals of US$ 5.4 billion for HIV/AIDS, US$ 1.7 billion for malaria and US$ 0.7 billion for TB in 2014. To provide some context for these amounts, the latest estimates (for 2013) of the burden of disease in terms of disability-adjusted life years (DALYs) lost due to illness and death are 69 million for HIV/AIDS, 50 million for malaria and 65 million for TB.

The cost per patient treated is usually in the range of US$ 100–1000 for drug-susceptible TB and US$ 2000–20 000 for MDR-TB.

Health financing data from national health accounts provide insights into the current status of progress towards universal health coverage, as discussed in Chapter 6.

KEY REPORTING FACTS


can provide insights into progress towards universal health coverage (UHC), which is necessary to achieve the End TB Strategy milestones set for 2020 and 2025 (Chapter 2). Measurement of costs faced by TB patients and their households is also required to assess progress towards one of the three high-level indicators of the End TB Strategy; that is, the percentage of TB patients and their households who face catastrophic costs as a result of TB disease. The milestone of zero set for this indicator for 2020 requires progress in terms of both UHC and social protection (included under Pillar 2 of the End TB Strategy). These two topics — analysis of health financing data, and measurement of costs faced by TB patients and their households — are covered in Chapter 6.

Further country-specific data on TB financing can be found in finance profiles that are available online.1

### 7.1 Estimates of funding required for a full response to the global TB epidemic, 2016–2020

The latest estimates of the funding required for a full response to the global TB epidemic, to achieve the End TB Strategy milestones for 2020, have been set out in the Stop TB Partnership’s Global Plan to End TB, 2016–2020.2 Worldwide, the amount for implementation of TB prevention, diagnostic and treatment interventions rises from almost US$ 9.5 billion in 2016 to US$ 14 billion in 2020 (Fig 7.1). Most of this total (75%) is for diagnosis and treatment of drug-susceptible TB, which grows from US$ 7.4 billion in 2016 (US$ 6.4 billion in low- and middle-income countries) to US$ 9.7 billion in 2020. However, the amount for drug-resistant TB doubles from US$ 1.8 billion in 2016 to US$ 3.6 billion in 2020.3 Relatively small amounts are needed for TB/HIV interventions, mainly because the figure does not include the funding needed for antiretroviral therapy for HIV-positive TB patients.4 An additional US$ 9 billion is needed for TB research and development over the 5-year period (data not shown; this topic is discussed further in Chapter 8).

Of the total of US$ 58 billion over 5 years (excluding research and development), US$ 52 billion was estimated to be required in low- and middle-income countries (growing from US$ 8.3 billion in 2016 to US$ 12.3 billion in 2020). Within this group of countries, estimates of the funding that could be mobilized from domestic and international donor sources were restricted to countries eligible to apply to the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund).5 For eligible countries, the funding required over 5 years amounts to US$ 29 billion; it was estimated that about US$ 16 billion of this amount could be mobilized from domestic sources and that the remainder (an average of US$ 2.6 billion per year) would need to come from international donors.

The Global Plan to End TB did not attempt to assess the broader investments required to increase the overall coverage and quality of health-care services, and to remove financial barriers to accessing care. Such investments are needed for many essential preventive, treatment and care interventions, not only for TB. Progress on these fronts is critical, as explained in Chapter 2, reflected in Pillar 2 of the End TB Strategy and discussed in Chapter 6. The costs in the Global Plan can thus be seen as the financial resources required for Pillars 1 and 3 of the End TB Strategy.

### 7.2 TB funding, overall and by category of expenditure and source of funding, 2006–2016

Data reported by NTPs to WHO since 2006 were used to analyse funding trends over the period 2006–2016 in 126 countries (Table 7.1). These countries accounted for 97% of the global number of TB cases reported in 2015, and included 126 low- and middle-income countries. The methods used to collect, review and analyse financial data are summarized in Box 7.1.

In these 126 countries, funding for TB prevention, diagnosis and treatment reached US$ 6.6 billion in 2016, up from US$ 6 billion in 2015 and almost double the US$ 3.5 billion that was available in 2006 (all figures are in constant values for 2016, see Fig. 7.2). Of the total of US$ 6.6 bil-

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1 www.who.int/tb/data
3 The burden of drug-resistant TB (in terms of cases per year) is not projected to increase between 2016 and 2020. Increased funding is required to close detection and treatment gaps (see also Chapter 4).
5 Countries not eligible to apply to the Global Fund include Brazil, China, the Russian Federation and about half of the other 52 countries classified as upper middle income.
### Table 7.1

126 countries included in analyses of TB financing, by income group and WHO region, 2016\(^a\)\(^b\)

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-income (30/31 countries representing 13% of notified cases globally in 2015)</td>
<td>Benin, Burkina Faso, Burundi, Central African Republic, Chad, DR Congo, Côte d’Ivoire, Ghana, Kenya, Lesotho, Mauritania, Nigeria, Senegal, Sierra Leone, South Sudan, Togo, Uganda, UR Tanzania, Zimbabwe</td>
</tr>
<tr>
<td>Lower-middle-income (48/52 countries representing 58% of notified cases globally in 2015)</td>
<td>Cabo Verde, Cameroon, Congo, Angola, Botswana, Gabon, Mauritius, Namibia, South Africa</td>
</tr>
<tr>
<td>Upper-middle-income (48/55 countries representing 26% of notified cases globally in 2015)</td>
<td>South Africa</td>
</tr>
<tr>
<td>BRICS (48% of notified cases globally in 2015)</td>
<td>Angola, Central African Republic, Congo, DR Congo, Ethiopia, Kenya, Lesotho, Liberia, Mozambique, Namibia, Nigeria, Sierra Leone, UR Tanzania, Zambia, Zimbabwe</td>
</tr>
<tr>
<td>25 high-burden countries excluding BRICS (37% of notified cases globally in 2015)</td>
<td>Brazil</td>
</tr>
</tbody>
</table>

\(^a\) Analyses focus on low and middle-income countries.

\(^b\) Additional countries included in trend analyses of TB financing compared with those included in previous global reports are shown in bold.
lion, most (US$ 4.4 billion, 67%) is for the diagnosis and treatment of drug-susceptible TB. However, that amount still falls considerably short of the US$ 6.4 billion estimated to be needed for low- and middle-income countries in the Global Plan (Section 7.1).

Funding for MDR-TB was US$ 1.7 billion in 2016, and this amount has been comparatively stable since 2014, following a marked increase in 2010–2014 (Fig. 7.2). Trends in funding for MDR-TB have been driven by the BRICS (Brazil, Russian Federation, India, China and South Africa) group of countries (Fig. 7.3), with just over one third of reported funding for MDR-TB accounted for by the Russian Federation in 2016 (Table 7.2, Fig. 7.2). Given the large gaps in detection that remain for MDR-TB, and the gaps between the numbers of cases detected and started on treatment (Chapter 4), much more funding is required for MDR-TB globally and in most of the high MDR-TB burden countries. Based on the estimates in the Global Plan (Section 7.1), funding for MDR-TB needs to double between 2016 and 2020.

A detailed breakdown of the funding estimated to be required for drug-susceptible TB, MDR-TB and collaborative TB/HIV activities in 2016, based on NTPs’ assessments of their needs, is shown for the 30 high TB burden countries (TB HBCs) in Table 7.2.

Overall, domestic funding for the TB-specific budgets of NTPs accounts for the largest single share of funding, followed by funding for inpatient and outpatient care (Fig. 7.4). Since most (91%) of the funding estimated to be used for inpatient and outpatient care is accounted for by middle-income countries, it can be assumed that virtually all of this funding is from domestic sources (international donor funding for inpatient and outpatient care is only likely to occur in low-income countries, via general budget support to the health sector). Based on this assumption, about 84% of the estimated funding of US$ 6.6 billion in 2016 is from domestic sources.

1 Chapter 2 explains how the updated list of TB HBCs to be used by WHO in 2016–2020 was defined.
WHO began monitoring government and international donor financing for TB in 2002. All data are stored in the WHO global TB database. The standard methods used to compile, review, validate and analyse these have been described in detail elsewhere; this box provides a summary.

Each year, WHO requests all low- and middle-income countries to report:

- the funding they estimate will be needed for TB prevention, diagnosis and treatment in their current fiscal year, by category of expenditure and source of funding; and
- expenditures for the most recently completed fiscal year, also by category of expenditure and source of funding.

In the 2016 round of global TB data collection, the fiscal years were 2016 and 2015. Consistency in categories of expenditure used to report budget and expenditure data has been maintained as far as possible to enable monitoring of trends. For low- and middle-income countries, the categories of expenditure for drug-susceptible TB used in the 2016 round of global TB data collection were laboratory infrastructure, equipment and supplies; NTP staff at central and subnational levels (e.g. NTP managers and provincial or district TB coordinators); first-line drugs; programme costs (e.g. management and supervision activities, training, policy development, meetings, purchase of office equipment and vehicles, recording and reporting of notifications and treatment outcomes, advocacy and communication, public–private mix activities and community engagement); and operational research, including surveys. For MDR-TB, two expenditure categories were used: second-line drugs, and programme costs specifically related to MDR-TB. Starting in 2015, a separate category for patient support was included, linked to the emphasis on financial and social protection in the End TB Strategy. There is also a separate category for collaborative TB/HIV activities. A breakdown of the total amount of available funding is requested in four categories: domestic funding excluding loans; external loans, also considered domestic funding; the Global Fund; and grant financing from sources other than the Global Fund.

As in previous years, all high-income countries were requested to report funding requirements and expenditures in total, without any breakdown by category of expenditure or source of funding.

All countries (irrespective of income level) were asked to report on the use of inpatient and outpatient care required for treatment of people with drug-susceptible and MDR-TB on a per-patient basis (i.e. the average number of days spent in hospital, and the average number of outpatient visits to a health facility). These data can be based on actual use data (preferable), or on the expected use based on the typical approach used to deliver treatment (which may be defined in national policy documents). They are combined with other data to estimate the financial resources used for TB treatment that are not reflected in NTP-reported budgets and expenditures (further details are provided below).

Core methods used to review and validate data have remained consistent since 2002. They include:

- **routine checks for plausibility and consistency, including validation checks that are built into the online reporting system** – examples of validation checks are checks for implausibly large year-to-year changes (e.g. in total reported funding by source and by category of expenditure), or implausibly high or low values of funding for drugs relative to the number of TB patients (that differ substantially from prices quoted by the Global TB Drug Facility);
- **discussions with country respondents to resolve queries**; and
- **triangulation with other data sources** – such sources include estimates of unit costs from independent economic evaluations and funding proposals (known as concept notes) submitted to the Global Fund; comprehensive budgets for national strategic plans are now an essential requirement for funding applications to the Global Fund.

Since 2014, an extra question about the average cost of drugs per patient treated has been asked, to allow reviewers to better assess the validity of budgets reported for first- and second-line drugs, and to identify whether reported budgets include funding for buffer stocks.

In 2016, additional efforts to improve the quality of financial data reported to WHO included presentations and discussions with NTP staff during workshops on the development of national strategic plans or TB modelling.

In review and validation of data, particular attention has always been given to HBCs. A summary of data validation methods used for the 30 TB HBCs is shown in Table B7.1.1.

Usually, TB funding reported by NTPs does not include the financial costs associated with the inpatient and outpatient care required during treatment. Since many detailed costing studies in a wide range of countries show that these costs account for a large share of the cost of treating someone with TB, WHO analyses of TB financing have always included estimates of the funding used for both inpatient and outpatient care.

WHO estimates the funding used for inpatient and outpatient care of TB patients by multiplying the number of outpatient visits and days of inpatient care per patient (reported by NTPs each year) by the cost per bed day and per clinic visit available from the WHO CHOosing Interventions that are Cost-Effective (WHO-CHOICE) database, and then by the reported number of TB patients notified or projected to be notified. This is done separately for drug-susceptible TB and MDR-TB. Where possible, estimates are compared with hospital and clinic expenditure data for drug-susceptible and MDR-TB that are being tracked through the System of health accounts (SHA). In 2016, SHA data were available for 27 countries (including the six HBCs shown in Table B7.1.1), and were used in preference to estimates based on reported use
and unit costs estimates from WHO-CHOICE. In a few cases, there were large discrepancies (e.g. Cambodia, the Philippines and the United Republic of Tanzania). Further discussions with country focal points for national health account data are needed in order to better understand the reasons for these discrepancies.

Expanded implementation of SHA and associated validation against existing disease-specific tracking systems may also facilitate more comprehensive reporting of domestic funding for TB, especially reporting of the contributions from subnational administrative levels that are not always known or compiled at the national level. Although much of this contribution is likely to be for delivery of inpatient and outpatient care (which is included in current WHO estimates of domestic funding for TB, as explained above), reporting of funding from these levels (including TB-specific budgets) is a particular challenge in large countries with decentralized systems. Examples for TB include Indonesia, Nigeria and South Africa.


:: TABLE B7.1.1

Methods used to review and validate financing data reported by NTPs, 30 high TB burden countries

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>UNIT COST DATA AVAILABLE FROM INDEPENDENT ECONOMIC EVALUATION</th>
<th>TRIANGULATION OF WHO TB DATA WITH OTHER SOURCES</th>
<th>NATIONAL HEALTH ACCOUNT DATA, FOR COMPARISON OF INPATIENT AND OUTPATIENT CARE EXPENDITURES FOR DRUG-SUSCEPTIBLE AND MDR-TB</th>
<th>COSTED NATIONAL STRATEGIC PLAN SUBMITTED AS PART OF A FUNDING APPLICATION TO THE GLOBAL FUND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Brazil</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Cambodia</td>
<td>yes</td>
<td>yes, 2012</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>China</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Congo</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>DR Congo</td>
<td>no</td>
<td>yes, 2014</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>India</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
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<td>Indonesia</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Kenya</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Lesotho</td>
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<td>no</td>
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<td>Liberia</td>
<td>no</td>
<td>no</td>
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</tr>
<tr>
<td>Mozambique</td>
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<td>no</td>
<td>yes</td>
<td>yes</td>
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</tr>
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<td>yes</td>
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</tr>
<tr>
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<td>no</td>
</tr>
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<td>yes, 2013</td>
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<tr>
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<td>Zimbabwe</td>
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<td>no</td>
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Table 7.2

Reported NTP budget by intervention area and estimated cost of inpatient and outpatient care for drug-susceptible (DS-TB) and MDR-TB, 30 high TB burden countries, 2016 (current US$ millions)

<table>
<thead>
<tr>
<th>Country</th>
<th>National Strategic Plan Budget</th>
<th>Resources Required for Inpatient and Outpatient Care</th>
<th>Resources Required for TB Care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>DS-TB</td>
<td>MDR-TB</td>
</tr>
<tr>
<td>Angola</td>
<td>22</td>
<td>19</td>
<td>2.0</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>52</td>
<td>49</td>
<td>2.3</td>
</tr>
<tr>
<td>Brazil</td>
<td>60</td>
<td>48</td>
<td>11</td>
</tr>
<tr>
<td>Cambodia</td>
<td>29</td>
<td>26</td>
<td>1.9</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>1.8</td>
<td>1.4</td>
<td>0.06</td>
</tr>
<tr>
<td>China</td>
<td>372</td>
<td>348</td>
<td>24</td>
</tr>
<tr>
<td>Congo</td>
<td>3.8</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>DPR Korea</td>
<td>30</td>
<td>27</td>
<td>3.3</td>
</tr>
<tr>
<td>DR Congo</td>
<td>60</td>
<td>51</td>
<td>5.7</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>81</td>
<td>54</td>
<td>17</td>
</tr>
<tr>
<td>India</td>
<td>280</td>
<td>209</td>
<td>65</td>
</tr>
<tr>
<td>Indonesia</td>
<td>123</td>
<td>101</td>
<td>15</td>
</tr>
<tr>
<td>Kenya</td>
<td>59</td>
<td>45</td>
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</tr>
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<td>5.3</td>
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<td>Liberia</td>
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<td>Myanmar</td>
<td>69</td>
<td>51</td>
<td>16</td>
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<tr>
<td>Namibia</td>
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<td>1.3</td>
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<td>Nigeria</td>
<td>257</td>
<td>171</td>
<td>74</td>
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<td>Pakistan</td>
<td>62</td>
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<td>19</td>
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<td>Papua New Guinea</td>
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<td>7.8</td>
<td>3.0</td>
</tr>
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<td>Philippines</td>
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<td>Russian Federation a</td>
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<td>766</td>
<td>583</td>
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<td>Sierra Leone</td>
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<td>7.6</td>
<td>0.87</td>
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<td>South Africa</td>
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<td>68</td>
</tr>
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<td>Thailand</td>
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<td>27</td>
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</tr>
<tr>
<td>Viet Nam</td>
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<td>55</td>
<td>14</td>
</tr>
<tr>
<td>Zambia</td>
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<td>9.0</td>
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</tr>
<tr>
<td>Zimbabwe</td>
<td>28</td>
<td>23</td>
<td>1.1</td>
</tr>
</tbody>
</table>

30 high TB burden countries: 3747, 2573, 977, 198, 966, 506, 5219

Blank cells indicate data not reported.
— indicates values that cannot be calculated.
1 No amount is shown for China and the Russian Federation because the NTP budgets reported by those countries include all budgets for inpatient and outpatient care.
2 In the Russian Federation, the staff and infrastructure reported for TB care and control were allocated to DS-TB (54%) and MDR-TB (46%) by WHO based on the proportion of beddays used by DS-TB and MDR-TB patients.
International donor funding for the TB-specific budgets of NTPs has generally increased year-on-year since 2006, and reached US$1.0 billion in 2016. The exception was 2013–2014, when amounts of donor funding reported by NTPs dropped by US$150 million (US$0.9 billion to US$0.75 billion). This change was not as marked as the fall indicated by the creditor reporting system (CRS) of the Organisation for Economic Co-operation and Development (OECD) (see Box 7.2). Some possible reasons for this situation are that the OECD data include transfers to entities other than NTPs, and that the lists of countries included do not fully overlap.

Global aggregates for countries reporting financing data to WHO conceal substantial variation among countries in the share of funding from domestic and international sources (Fig. 7.5, Table 7.3). Domestic funding dominates (representing 91–96% of the funding available to NTPs in 2016) in three country groups (that are not mutually exclusive): BRICS, upper middle-income countries, and regions outside Africa and Asia. In other country groups, international donors (especially the Global Fund) are the most important source of funding and are responsible for most of the growth in TB funding in the past decade, especially in the 25 TB HBCs outside BRICS (listed in Table 7.1) and the

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**Fig. 7.5**

Funding for NTP budgets from domestic sources and international donors, 2006–2016, 9 country groups (constant 2016 US$ billions)

- **a. BRICS**
- **b. 25 HBCs excluding BRICS**
- **c. Rest of world**
- **d. Low-income countries**
- **e. Lower-middle-income countries**
- **f. Upper-middle-income countries**
- **g. Africa**
- **h. Asia**
- **i. Other regions**

### Notes

1. Rest of the world includes 96 countries that are not in the list of 30 high TB burden countries.
2. Asia includes the WHO regions of South-East Asia and the Western Pacific.
3. Other regions consist of three WHO regions: the Eastern Mediterranean Region, the European Region, and the Region of the Americas.
4. This includes the Global Fund.
Not all international donor funding that is provided for TB prevention, diagnosis and treatment is channelled through NTPs. The creditor reporting system (CRS) of the OECD is the most comprehensive source of information about international donor funding. Funding data (both commitments and disbursements) are provided by 31 multilateral donor organizations, the 26 countries that are members of the OECD’s Development Assistance Committee and a further two non-committee members (Kuwait and the United Arab Emirates).

Disbursement data include both direct transfers to countries and the provision of goods and services, such as in-kind transfers or technical assistance. Data on gross disbursements\(^a\) for TB (code 12263: Tuberculosis control) received by non-OECD countries over the period 2004-2014 were analysed. Funding for TB that flows from one OECD member to an institution or government within the OECD, such as grants from the United States (US) National Institutes for Health to the United Kingdom, is not captured in the CRS. Also, government contributions to multilateral organizations are not attributed to the government of origin but only to the multilateral organization.\(^b\)

**Fig. B7.2.1** shows trends in international donor funding between 2004 and 2014, for four major categories. The total from all sources in 2014 was US$ 0.7 billion, up from US$ 0.1 billion in 2004. In 2014, 57% of international TB donor funding was from the Global Fund (US $ 0.4 billion) and the next largest contributor was the US government (32%; US $ 247 million). Given that about one third of the contributions to the Global Fund are from the US government, about half of international donor funding globally originated from the US government in 2014.\(^c\) The remaining funding came from other countries (9%) and multilateral organizations (2%), among which the largest donors were the governments of the United Kingdom (5%) and Japan (2%).

Throughout the period 2004–2014, the Global Fund was consistently the largest provider of international donor funding, but there was a striking drop of 44% from a peak of US$ 0.8 billion in 2013 to US$ 0.44 billion in 2014. This may reflect the transition to a new funding model that started in 2013, and some associated delays in approving and disbursing funds. Disbursements from the US government steadily increased over the period 2004–2014, reaching a peak of US$ 247 million in 2014.

Asia and Africa received the vast majority of international donor funding (Fig. B7.2.2), and the decline in funding from the Global Fund was evident in 2013–2014 in four geographical subregions. These reductions were partly mitigated by increased funding from the US government in Asia, Africa and Europe (but not the Americas).

A comparison of international donor funding for HIV/AIDS (coded as sexually transmitted disease [STD] control within the OECD reporting system), malaria and TB is shown in **Fig. B7.2.3**. In 2014, non-OECD countries received US$ 5.4 billion for HIV/AIDS, US$ 1.7 billion for malaria and US$ 0.7 billion for TB. To provide some context for these amounts, the latest estimates (for 2013) of the burden of disease in terms of disability adjusted life years (DALYs) lost due to illness and death are 69 million for HIV/AIDS, 50 million for malaria and 65 million for TB.\(^d\) The decline in international donor funding observed for TB between 2013 and 2014 was also evident for HIV/AIDS, but not for malaria. The first- and second-ranking donors for TB and malaria are the Global Fund and the US government, whereas the order is reversed for HIV/AIDS (62% directly from the US government and 29% from the Global Fund).

\(^a\) As opposed to commitments, which may not materialize.

\(^b\) An important example is funding from the Global Fund to non-OECD countries, which is attributed to the Global Fund and not to the governments or other entities that contribute to the Global Fund.

\(^c\) It should be noted that contributions from the United States government captured in the OECD database are lower than official allocations. In 2014, the official allocation for TB was US$ 243 million and an additional US$ 15.4 million was allocated for TB/HIV via the President’s Emergency Plan for AIDS Relief (PEPFAR).

\(^d\) ghdx.healthdata.org/global-burden-disease-study-2013-gbd-2013-data-downloads
**FIG. B7.2.2**
International donor funding for TB prevention, diagnosis and treatment by region, 2004–2014

**FIG. B7.2.3**
# Table 7.3
Reported NTP budget, available funding for NTP budget from domestic and international donor sources, funding gap and share of NTP budget provided by domestic and international donor funding, 30 high TB burden countries, 2016 (current US$ millions)\(^a\)

<table>
<thead>
<tr>
<th>Country</th>
<th>Total National Strategic Plan Budget (A+B)</th>
<th>Domestic Funding (A)</th>
<th>International Donor Funding (B)</th>
<th>Share of Available Funding (A+B) Provided from Domestic Sources (%)</th>
<th>Share of Available Funding (A+B) Provided by International Donors (%)</th>
<th>Funding Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angola</td>
<td>22</td>
<td>8.4</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>13</td>
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<tr>
<td>Bangladesh</td>
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<td>45</td>
<td>12</td>
<td>88</td>
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<tr>
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<td>99</td>
<td>1.2</td>
<td>13</td>
</tr>
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<td>21</td>
<td>79</td>
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<td>0.27</td>
<td>0.27</td>
<td>0.27</td>
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</tr>
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<td>98</td>
<td>1.7</td>
<td>4.4</td>
</tr>
<tr>
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<td>2.6</td>
<td>15</td>
<td>85</td>
<td>0.8</td>
</tr>
<tr>
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<td>5.7</td>
<td>8.1</td>
<td>41</td>
<td>59</td>
<td>16</td>
</tr>
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<td>1.7</td>
<td>36</td>
<td>5</td>
<td>95</td>
<td>23</td>
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<td>Ethiopia</td>
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<td>41</td>
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<td>12</td>
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<td>20</td>
<td>80</td>
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<td>4.5</td>
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</tr>
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</tr>
<tr>
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<td></td>
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<td>28</td>
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<td></td>
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<tr>
<td><strong>30 high TB burden countries</strong></td>
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<td><strong>2421</strong></td>
<td><strong>758</strong></td>
<td><strong>76</strong></td>
<td><strong>24</strong></td>
<td><strong>484</strong></td>
</tr>
</tbody>
</table>

Blank cells indicate data not reported. — indicates values that cannot be calculated.

\(^a\) Funding gap reflects the anticipated gap for the year at the time a country reported data in the 2016 round of global TB data collection.

\(^b\) For Indonesia, available funding from domestic sources data are not shown because the Government of Indonesia is currently reviewing contributions from domestic sources.
group of low-income and lower middle-income countries (Fig. 7.5). International donors account for 75% of the total funding in 2016 in the group of 25 TB HBCs outside BRICS, 87% of funding in low-income countries and 60% of funding in lower middle-income countries. At the individual country level, international donors remain absolutely critical to funding for NTPs in most of the 30 TB HBCs (Table 7.3).

As noted above, funding reported by NTPs does not capture all international donor funding for TB. Donor funding is also provided to entities other than NTPs, including international and national governmental and nongovernmental organizations. A more comprehensive analysis of international donor funding for TB, including comparisons with HIV and malaria, is provided in Box 7.2, based on donor reports to the OECD. 1 Amounts for TB are much lower than donor contributions for HIV and malaria.

7.3 Funding gaps reported by national TB programmes, 2006–2016

Despite growth in funding from domestic and international donor sources, many NTPs continue to be unable to mobilize all the funding required for full implementation of their national strategic plans (Fig. 7.6). Funding gaps (i.e. the difference between assessments by NTPs of funding needs for TB prevention, diagnosis and treatment, and the actual amount of funds mobilized) have persisted, and in 2016 they amounted to a total of US$ 0.8 billion. This is less than half of the gap of US$ 1.7 billion that exists between the US$ 8.3 billion estimated to be needed in low- and middle-income countries in 2016 according to the Global Plan (Section 7.1) and the US$ 6.6 billion available in 2016 (Section 7.2). The difference can be explained by the fact that, in many countries, national strategic plans for TB are less ambitious than the targets set in the Global Plan (Section 7.1).

Lower middle-income countries account for the largest reported funding gaps (almost US$ 0.5 billion in 2016). Geographically, almost half of the total reported funding gap is accounted for by countries in the WHO African Region, with the largest gaps reported by Ethiopia and Nigeria (Table 7.3). Funding gaps were relatively small in upper middle-income countries in 2016 (Fig. 7.6), and have fallen in recent years. This trend is mostly explained by larger reductions in the funding gaps reported by China, Kazakhstan and the Russian Federation, which reported funding gaps in 2006–2011 but negligible or zero gaps thereafter. Funding gaps reported by low-income countries have fallen since 2012, reflecting a transition of some countries out of the low-income country group and into the group of middle-income countries.

Of the US$ 0.8 billion funding gap reported by NTPs in 2016, US$ 0.63 billion is for drug-susceptible TB and US$ 0.14 billion is for MDR-TB. Relative to total funding needs, the funding gap is larger for drug-susceptible TB than for MDR-TB. Domestic funding accounts for a larger share of the funding for MDR-TB than for drug-susceptible TB: this is not surprising given that most of the high MDR-TB burden countries are middle- or high-income countries.

7.4 Unit costs of treatment for drug-susceptible and multidrug-resistant TB, 2015

The cost per patient treated in 2015 for drug-susceptible and MDR-TB was estimated for 117 countries and 82 countries, respectively.  2 All 30 countries in the lists of TB and

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1 Out-of-pocket expenditures are also not included in NTP reports. These are discussed in more detail in Chapter 6.

2 Analysis for drug-susceptible TB was limited to countries that notified at least 100 TB cases in 2015. For MDR-TB, estimates were restricted to countries that reported at least 10 patients on second-line treatment for MDR-TB.
**FIG. 7.7**
Estimated cost per patient treated for drug-susceptible TB in 117 countries, 2015

- Limited to countries with at least 100 notified patients in 2015.

**FIG. 7.8**
Estimated cost per patient treated for MDR-TB in 82 countries, 2015

- Limited to countries with at least 20 patients on second-line treatment in 2015.
Methods used to estimate the cost per patient treated for drug-susceptible and MDR-TB

Two main data sources were used to estimate the cost per patient treated for drug-susceptible TB and MDR-TB. The first was the validated expenditure data reported by NTPs that are stored in the WHO global TB database. The second was country-specific estimates of the unit costs of bed days and outpatient visits available from the WHO-CHOICE model and associated database (managed by the WHO Health Governance and Financing Department). In the few instances where no expenditure data could be reported, information about the total funding available was used as a proxy for expenditures. Also, for a few countries, WHO-CHOICE estimates were replaced with estimates of unit costs obtained directly from recent studies or discussions with experts.

Costs were calculated separately for drug-susceptible TB and MDR-TB. In each case, the numerator was the total estimated cost of treatment, which has two main parts: the national expenditures reported by the NTP, and the costs associated with the use of health services for TB patients. As explained in Box 7.1, national NTP expenditures are reported annually to WHO using the online WHO global TB data collection system, and are then reviewed and validated. Categories of expenditure considered as costs for MDR-TB were second-line drugs and all other inputs or activities implemented for the programmatic management of MDR-TB. All other categories (with the exception of collaborative TB/HIV activities) were assumed to be for drug-susceptible TB.

For almost all countries, the total costs associated with use of inpatient and outpatient care were calculated using information about the typical number of days of inpatient care and outpatient visits required on a per-patient basis during treatment (reported separately for drug-susceptible TB and MDR-TB by NTPs) combined with WHO-CHOICE unit cost estimates, multiplied by the number of patients treated in a given year (based on notification data – see Chapter 4). Multiplying quantities of visits and bed days by their price estimates yields the total estimated cost of inpatient and outpatient services. For 27 countries (including six HBCs, see Box 7.1), TB inpatient and outpatient expenditures available from national health accounts were used instead of the estimated cost from this ingredients-based approach.

Unit costs were then calculated as the sum of 2015 NTP expenditures and total costs for use of inpatient and outpatient care, divided by the reported number of patients treated. Again, this calculation was carried out separately for drug-susceptible TB and MDR-TB.

MDR-TB HBCs were included in this analysis. Unit cost estimates are shown in Fig. 7.7 and Fig. 7.8, and analytical methods are summarized in Box 7.3.

7.4.1 Drug-susceptible TB

The cost per patient treated for drug-susceptible TB was generally in the range US$ 100–US$ 1000 (Fig. 7.7). In general, about 80% of this cost was accounted for by reported NTP expenditures, with the remainder being inpatient and outpatient care. There is a positive relationship between the cost per patient treated and gross domestic product (GDP) per capita, as well as the size of the patient caseload (indicating economies of scale, e.g. in China and India). In most (28/30) of the TB HBCs included in the analysis, the cost per patient treated for drug-susceptible TB was less than GDP per capita; the exceptions were Liberia and Sierra Leone.

The cost per patient treated was typically higher in countries in the WHO European Region and the WHO Region of the Americas. In countries of the former Soviet Union, the higher cost is partly explained by relatively lengthy hospitalizations, with admissions lasting up to an average of 75 days and accounting for about 40–60% of the total cost per patient. However, there are some striking examples of reductions in reliance on hospitalization. For example, the Russian Federation reported hospitalization of about 65% of TB patients with drug-susceptible TB in 2016, compared with 93% in 2014, and in Georgia the figures were 30% and 83%, respectively.

7.4.2 Multidrug-resistant TB

For MDR-TB, the cost per patient treated ranges from about US$ 2000–20 000 in most countries (Fig. 7.8). As with drug-susceptible TB, the cost per patient treated is related to GDP per capita. Following new WHO recommendations that shortened regimens of 9–12 months can be used for patients (other than pregnant women) with rifampicin-resistant or MDR pulmonary TB who do not have resistance to second-line drugs, at a cost of about US$ 1000 per person for the drug regimen, there is scope for the unit cost of second-line treatment for MDR-TB to fall in the coming years.


1 For further details about the new recommendations, see Chapter 4.
“Intensified research and innovation” is one of the three pillars of the WHO End TB Strategy. Its two main components are “discovery, development and rapid uptake of new tools, interventions and strategies” and “research to optimize implementation and impact, and promote innovations” (Chapter 2). The strategy sets targets for reductions in TB incidence and TB mortality by 2030 and 2035. Reaching these targets will require a major technological breakthrough by 2025, so that the rate at which TB incidence falls can be dramatically accelerated compared with historic levels between 2025 and 2035 (Chapter 2). A substantial increase in investment in TB research and development will be needed to achieve such a breakthrough. The Stop TB Partnership’s Global Plan to End TB, 2016–2020 estimates that about US$ 2 billion per year is needed during the period 2016–2020, compared with funding levels during the decade 2005–2014 that never exceeded US$ 0.7 billion per year.

This chapter provides an overview of progress in the development of new TB diagnostics, drugs and vaccines as of August 2016, based on recent publications and communications with and contributions from the secretariats of the relevant working groups of the Stop TB Partnership, and various stakeholders.

The Global Action Framework for TB Research (GAF), which has been developed by WHO to foster high-quality TB research across the spectrum, is profiled in Box 8.1.
WHO has developed Global Action Framework (GAF) to foster high-quality TB research across the spectrum (from basic science to implementation research), with the overall goal of ending the global TB epidemic. The GAF has two major dimensions: promoting research at country level and promoting research at global level, as summarized below.

Promoting research at country level
At country level, WHO encourages the establishment of a national TB research network of stakeholders (individuals and organizations) that will drive research and innovation based on a shared desire to address the national TB epidemic. It is expected that the network will provide a systematic approach to addressing issues in TB prevention, diagnosis and treatment research. The approach should start with a situational analysis of the TB epidemic, and of the performance of the national TB control programme and wider health system, and mapping of research capacity. This should be followed by the development of a national TB research agenda to address identified gaps, the outcomes of which should inform TB care policy and practice. To support the development of such plans for research, WHO’s Global TB Programme has developed a toolkit to assist high and medium TB burden countries with each of these steps. Early adopters of this approach include Brazil, Ethiopia, the Russian Federation, South Africa and Viet Nam.

Promoting research at global level
WHO is promoting TB research by sharing innovations, organizing a variety of knowledge-sharing platforms, and facilitating the development of regional and global networks for research and capacity-building. This approach involves partnering with countries, organizations and institutions. WHO is also encouraging international collaboration between technologically advanced countries and those with limited resources, and is providing technical support to regional and global networks of TB researchers.

8.1 New diagnostics for TB

8.1.1 An overview of the diagnostics pipeline
The diagnostic technology landscape, which consists mostly of molecular tests, continues to look promising. An overview of the diagnostic pipeline for rapid molecular tests in August 2016 is shown in Fig. 8.1. The list of technologies is not necessarily complete, but does reflect technologies that have been documented in a recent report published by the Treatment Action Group. Technologies under development include tests to detect TB, drug resistance or TB and drug resistance combined.

At least three new commercial technologies – Epistem Genedrive, Epistem, United Kingdom; EasyNAT, Ustar Biotechnologies, China; and Molbio TrueNAT, Molbio, India – are intended for use at the microscopy level. However, available performance data for these tests are limited and highly variable, and to date no multi-centre evaluation or demonstration studies in different epidemiological settings have been conducted. Such studies are essential to generate the data required by WHO to assess and produce recommendations on their use, but funding and capacity to undertake the studies are limited. Several manufacturers have also indicated that they are developing centralized testing platforms suitable for high laboratory throughput. However, these platforms are not yet ready for field evaluation studies, and to be useful a large investment in sample transportation systems would be required.

Cepheid is developing a new platform called GeneXpert Omni, which is intended for point-of-care (POC) testing for TB and rifampicin-resistant TB using Xpert MTB/RIF cartridges or the next-generation Xpert Ultra cartridges. The device is expected to be smaller, lighter and less expensive than other currently available platforms for POC nucleic acid detection. The platform is expected to come with a built-in 4-hour battery and an auxiliary battery that provides an additional 12 hours of run time. Delays in the development of the GeneXpert Omni mean that the instruments are not likely to be available before the second half of 2017. The new platform will be assessed for equivalence to the current GeneXpert platform before its launch. The GeneXpert Omni is expected to be an alternative to and complement the existing multi-module instruments.

Major gaps that remain in the diagnostic pipeline include tests for the diagnosis of TB in children, rapid drug susceptibility tests for drugs that may be part of new treatment regimens, tests that accurately predict progression from latent TB infection (LTBI) to active TB disease, and alternatives to TB microscopy and culture for treatment monitoring. In addition, experience with GeneXpert has made it clear that any new technology will need to be rolled out with an entire set of interventions, including comprehensive training, quality assurance, implementation plans, data connectivity, and service and maintenance support.

8.1.2 TB diagnostic tests reviewed by WHO in 2016

WHO reviewed three diagnostic technologies in 2016: the loop-mediated isothermal amplification test for TB (referred to as TB-LAMP); line probe assays (LPAs) to test for resistance to first-line anti-TB drugs; and LPAs to test for resistance to second-line anti-TB drugs. These technologies are discussed below.

**Loop-mediated isothermal amplification test for TB**

TB-LAMP – developed by Eiken, Japan – is a manual test that takes less than 1 hour. Results can be read with the naked eye under ultraviolet light, and the TB-LAMP instrument can be used at the peripheral health centre level, which is where sputum smear microscopy is often performed. The level of training of staff required to perform the test is also similar to that needed for microscopy. TB-LAMP performs better than sputum smear microscopy, detecting at least 40% more patients with pulmonary TB; this is an increase comparable to other rapid tests that have been recommended by WHO in recent years. The test does not detect drug resistance and is therefore only suitable for testing of smear-positive specimens. It can also be used to test cultured isolates of Mycobacterium tuberculosis. Direct testing of sputum smear-negative specimens is not recommended. Further details are available online.

**Line probe assays to test for resistance to first-line anti-TB drugs**

Two LPAs for the detection of resistance to the first-line drugs isoniazid and rifampicin have been developed, one by the Nipro Corporation, Japan and the other by Hain Lifesciences, Germany. These LPAs can provide results on drug resistance within days, compared with up to 4 weeks for phenotypic culture-based testing.

Following review of the latest evidence, WHO recommends that both these LPAs can be considered for use as an initial test to detect resistance to rifampicin and isoniazid in smear-positive specimens. They can also be used to test cultured isolates of Mycobacterium tuberculosis. Direct testing of sputum smear-negative specimens is not recommended. Further details are available online.

**Line probe assay to test for resistance to second-line anti-TB drugs**

An LPA for the detection of resistance to second-line anti-TB drugs (fluoroquinolones and injectables) has been developed by Hain Lifesciences, Germany. Following review of the latest evidence, WHO recommends that this LPA can be considered as an initial test for resistance to second-line anti-TB drugs, given its ability to provide rapid results, especially when used for the direct testing of sputum specimens from patients with confirmed multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB. The speed of testing
is critical to allow for the time-sensitive step of triaging patients between the standardized short regimen for MDR-TB (which is recommended for use only in patients who do not have second-line drug resistance). If the LPA result is negative, WHO recommends that phenotypic culture-based testing may be necessary, especially in settings with a high pretest probability for resistance to fluoroquinolones or second-line injectable drugs, or both. Further details are available online.1

8.1.3 Technologies scheduled for evaluation in 2017 Xpert Ultra

A new version of the Xpert MTB/RIF assay, called Xpert Ultra, is in development by Cepheid. The current assay has been modified with the aim of improving its sensitivity for the detection of TB and its specificity in the detection of resistance to rifampicin; it can be used in the Omni platform (described above).

In early 2017, WHO will initiate a two-step evaluation process of Xpert Ultra based on data from evaluations by the Foundation for Innovative New Diagnostics (FIND). The first step is a rapid noninferiority (i.e. equivalence) study that will compare the new Xpert Ultra assay with the current Xpert MTB/RIF assay. If noninferiority is demonstrated, the Xpert Ultra assay will be recommended as a replacement for the current Xpert MTB/RIF assay. Later in 2017, the second evaluation step will involve multicountry studies.

Updated critical concentrations for culture-based drug susceptibility testing

Phenotypic methods to detect resistance to anti-TB drugs are based on assessment of the ability of the M. tuberculosis complex (MTBC) to grow in culture media containing critical concentrations (CC) of specific anti-TB agents (which indicates resistance) or, conversely, its inability to grow in that media (which indicates susceptibility). Susceptibility is used as a proxy for successful treatment outcome, and resistance as a proxy for treatment failure.

New drugs for the treatment of MDR-TB have been recommended by WHO (Section 8.2), and other drugs are being repurposed (notably linezolid and clofazamine) in the shortened MDR-TB regimens. Methods for testing for susceptibility to these drugs are therefore needed. Other anti-TB agents – for example, the fluoroquinolones, second-line injectable agents, thioamides, cycloserine and pyrazinamide – are becoming increasingly important in the treatment of drug-resistant TB; hence, there is a need for the CCs of these anti-TB agents to be re-evaluated as well.

WHO has initiated a systematic approach to aggregating and analysing data (published and unpublished) to assess the association of CC or minimal inhibitory concentration with epidemiological cut-offs and patient outcomes. Through this approach, WHO expects to be able to revise current CCs and validate new CCs, especially for the new and repurposed drugs.

Role of molecular sequencing as a reference standard for drug susceptibility testing

Drug resistance in MTBC is, possibly exclusively, due to mutations affecting the bacterial genome. Rapid molecular diagnostic tests have been developed for the simultaneous detection and identification of MTBC, and for the most common mutations causing resistance to specific drugs. However, for some anti-TB drugs, the association between the observed phenotypic resistance, mechanisms of resistance and the genetic basis of the phenotype are still poorly understood. Many new tools for sequencing and analysing the genome of MTBC have become widely accessible for the molecular detection of the mutations associated with drug resistance, but uncertainties remain about the correlation between specific single nucleotide polymorphisms (SNPs) and their expressed phenotypic resistance (as measured by both solid and liquid culture methods).

In 2017, WHO will evaluate the accuracy of genotypic drug susceptibility testing (DST) compared with the current phenotypic gold standards. WHO will also assess whether genotypic DST can replace phenotypic DST, at least for certain key drugs such as pyrazinamide and rifampicin.

8.1.4 Tests that predict progression from latent to active TB

Identifying and effectively treating people with LTBI who have no signs and symptoms of TB disease will be key to achieving the 2030 and 2035 targets of the End TB Strategy (Chapter 2). On average, 5–15% of those infected will develop active TB during their lifetime, typically within the first 2–5 years after the initial infection.

Current tests for LTBI are the interferon gamma release assays (IGRAs) and the tuberculin skin test (TST). These tests are immunity based, and have limited ability to predict disease or to identify which individuals with TB infection are likely to progress to active TB disease. They also have limited sensitivity in people with HIV infection, and cannot differentiate between recent and remote infection, or whether a person has been reinfected if re-exposed.

Current IGRA assays primarily detect a CD4 T-cell response. However, a new generation assay, the Quantiferon-TB Plus (QFT-Plus, Qiagen, Hilden, Germany), has been developed to stimulate gamma interferon production by both CD4 and CD8 T-cells. First results indicate that the CD8 T-cell response may be able to identify people at greater risk of progression to active TB.2


8.1.5 Diagnostic connectivity

The roll out of rapid diagnostic tools for TB patients allows for faster and more accurate testing. However, these benefits can be jeopardized if bottlenecks occur in the handling of samples and results. Streamlining the flow of data between testing, storage and sending of results is a critical sequence of steps that must accompany the roll out of new tests. For diagnostic systems to make a measurable impact on patient care, they should be able to communicate through a standardized digital interface, using technologies that are feasible regardless of the income level of the country or setting.1 Diagnostics connectivity solutions are now being monitored by WHO as a core indicator for laboratory strengthening under the End TB Strategy.

8.2 New drugs and drug regimens

Development of new drugs and regimens for the treatment of TB continues, with both advances and setbacks in 2015–2016. A new compound (Q203) entered a Phase I trial, but the development of AZDS847 by Astra-Zeneca was officially ended (due to lack of demonstrated anti-TB activity) and the development of TBA-354 was discontinued (due to signs of toxicity in the Phase I trial).2

The status of the pipeline for new anti-TB drugs in August 2016 is shown in Fig. 8.2. There are currently nine new or repurposed drugs in Phase I, II or III trials for the treatment of drug-susceptible TB, MDR-TB or LTBI. Of these, six are new compounds (bedaquiline, delamanid, PBTZ169, pretomanid, Q203 and sutezolid) and three are drugs that have already been approved or have been repurposed and are undergoing further testing (linezolid, rifampicin and rifapentine). These drugs are discussed below.

8.2.1 New compounds in development

**Bedaquiline**

After approval by the US Food and Drug Administration in December 2012 and WHO’s interim policy guidance on its use in June 2013,3 bedaquiline has been introduced in several countries for the treatment of severe forms of MDR-TB (Chapter 4).4,5 The safety and efficacy of bedaquiline as part of short MDR-TB regimens of 6 and 9 months duration, compared with the current standard of care recommended by WHO, is now being investigated in the second stage of the Phase III STREAM trial that started recruitment in March 2016. The first results are expected towards the end of 2020.

**Delamanid**

A conditional marketing authorization for delamanid was granted by the European Medicines Agency in April 2014. This was for the treatment of pulmonary MDR-TB in adult patients “when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability”. Interim guidance on the use of delamanid was issued by WHO in October 2014.6 The follow-up stage of a Phase III trial of the safety and efficacy of delamanid as an addition to an optimized background regimen (OBR) for the treatment of MDR-TB in adults was recently completed. It is anticipated that results will be published in 2018.

The use of delamanid in addition to OBR for treatment of MDR-TB in children is being investigated in Phase I and II trials. Partial results were presented in 2015.7

**PBTZ169**

A new series of piperazine-containing benzothiazinones (PBTZ) have shown highly potent activity against drug-susceptible and drug-resistant TB.8 PBTZ169 is compatible with all TB drugs and appears to have synergies with bedaquiline and clofazimine. A Phase I trial of PBTZ169 was completed in the Russian Federation in July 2016, and a second Phase I trial will be undertaken in Switzerland in 2017. A Phase IIa trial is expected to start towards the end of 2016 in the Russian Federation.

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2 TBA-354, belonging to the nitroimidazole class, was the first candidate to enter Phase I TB trials over the past 6 years. However, in a Phase I dose-escalating trial the drug was found to be associated with mild signs of neurotoxicity (repetitive uncontrolled eye movements and overactive reflexes, from which all affected study participants recovered). The TB Alliance announced the discontinuation of its development in March 2016. http://www.tballiance.org/news/phase-1-clinical-trial-tb-drug-candidate-tba-354-discontinued


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The global development pipeline for new anti-TB drugs, August 2016

| Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyrimidine amide. |
| 1 New chemical class |

Pretomanid

Pretomanid is a nitroimidazole developed by the Global Alliance for TB drug development (TB Alliance). It is currently being tested as part of three potential combination regimens for the treatment of both drug-susceptible and drug-resistant TB (further details in Section 8.2.2).

Q203

Q203 is a new compound of the imidazopyridine class developed by Qurient. It blocks the growth of TB bacilli by targeting the respiratory cytochrome bc1 complex, inhibiting the synthesis and homeostasis of adenosine triphosphate (ATP). Different levels of a single dose are being tested in a Phase I trial.

Sutezolid

Sutezolid (PNU-100480) is an oxazolidinone and an analogue of linezolid. Results from a study of early bactericidal activity presented in 2012 showed that this compound led to a significant reduction in counts of colony-forming units compared with the baseline level following 14 days of treatment. In August 2016, however, there was no further information available to WHO about its subsequent development.

8.2.2 Approved or repurposed drugs

Rifapentine

Investigation of the potential effectiveness of rifapentine in the treatment of drug-susceptible TB has continued, based on the encouraging results from TB Trial Consortium (TBTC) Studies 29 and 29X. TBTC Study 31/A5349 is investigating the possibility of shortening treatment of drug-susceptible pulmonary TB to 4 months by using rifapentine, with or without moxifloxacin. Recruitment started in January 2016.

Rifampicin

A recent 2-month study testing the safety of high doses of rifampicin together with standard treatment for drug-susceptible TB showed no significant increase in adverse events at doses of 10 mg/kg, 15 mg/kg and 20 mg/kg.2

8.2.3 New regimens for the treatment of drug-susceptible or drug-resistant TB

Besides individual compounds, new combinations of drugs are being tested in several Phase II or Phase III trials.

The TB Alliance is investigating the efficacy, safety and tolerability of pretomanid in combination with moxifloxacin and pyrazinamide (PaMZ). Following the encour-
aging results of the 2-month NC-002 Phase IIb trial, the STAND trial was launched in February 2015. This is a Phase III trial of the safety and efficacy of Pa(100 mg)MZ for 4 months, Pa(200 mg)MZ for 4 months and Pa(200 mg)M2 for 6 months in patients with drug-susceptible TB; and of Pa(200 mg)MZ for 6 months in patients with drug-resistant TB. In late 2015, enrolment was temporarily suspended due to three deaths related to high liver toxicity. Subsequently, the TB Alliance has been working with regulatory authorities and the trial’s data safety and monitoring committee to determine whether to restart enrolment, and if so, when to do so.

A Phase IIb trial (NC-005) to test all-oral combination regimens started in October 2014. The regimens being tested are bedaquiline (at two different doses), pretomanid and pyrazinamide for patients with drug-susceptible TB, and the same drugs in combination with moxifloxacin for patients with MDR-TB. Enrolment was completed towards the end of 2015, and results are expected in late 2016.

The NiX-TB trial is being implemented by the TB Alliance in South Africa. It is investigating the safety and efficacy of a 6-month combination of bedaquiline, pretomanid and linezolid in patients with extensively drug-resistant TB (XDR-TB). The primary end-point is the incidence of bacteriologic failure (relapse or clinical failure) 6 months after completion of treatment, with long-term follow-up for 24 months after the end of treatment. Alongside this trial, the efficacy of escalating doses of linezolid in patients with drug-susceptible TB over a period of 2 weeks is also being investigated. Results will inform adjustments to the dosing of linezolid in the NiX-TB trial as well as other regimens that include linezolid.

The endTB and TB-PRACTECAL trials are scheduled to start around the end of 2016. The former is a Phase III trial funded by UNITAID, and implemented by Partners in Health and Médecins Sans Frontières (MSF). It will compare several regimens for treatment of MDR-TB or XDR-TB with the current WHO standard of care. The regimens being tested contain bedaquiline or delamanid (or both), moxifloxacin or levofloxacin, and pyrazinamide plus linezolid or clofazimine (or both), in various combinations. The TB-PRACTECAL trial is a Phase I/II adaptive trial to evaluate the safety and efficacy of 6-month regimens that contain bedaquiline, pretomanid and linezolid, with or without moxifloxacin or clofazimine, for the treatment of adults with MDR-TB or XDR-TB. The trial is funded by MSF and will be conducted in Belarus, Uzbekistan, and potentially in countries in southern Africa.

The NeXt study is an open label trial of a 6-9 month injection-free regimen containing bedaquiline, ethionamide or high-dose isoniazid, linezolid, levofloxacin, and pyrazinamide, compared with the WHO-recommended 12-month shorter regimen for MDR-TB treatment. Recruitment started in South Africa in 2016.

8.2.4 Treatment of latent TB infection
Several studies evaluating shorter regimens for LTBI are being implemented, particularly for prevention of LTBI in people living with HIV. ACTG A5279 is evaluating the safety and effectiveness of ultra-short-course rifapentine or isoniazid (or both) for the prevention of active TB in HIV-positive people with LTBI. Rifapentine (at a dosage based on weight) in combination with 300 mg of isoniazid for 1 month is being compared with 300 mg of isoniazid for 9 months. Results are expected in the last quarter of 2017.

The “Weekly High dose Isoniazid and rifapentine (P) Periodic Prophylaxis for TB” trial, known as WHIP3 TB, is due to start by the end of 2016. It will evaluate a 3-month regimen of high dose rifapentine plus isoniazid for people living with HIV, administered either as a single round or given annually. It will be implemented in South Africa, Mozambique and Ethiopia, in two parts. Part A will compare a single round of weekly high dose rifapentine plus isoniazid for three months (3HP) to six months of daily isoniazid (6H); Part B will compare periodic 3HP (p3HP) to a single round of 3HP.

Two trials to investigate drugs or regimens for the prevention of TB in contacts of MDR-TB patients are being implemented or are planned. The V-QUIN MDR study is assessing 6 months of daily levofloxacin for household contacts of patients with MDR-TB. It is being conducted in Viet Nam and recruitment started in March 2016. The TB-CHAMP study is a multicentre trial to evaluate the efficacy of levofloxacin in children aged 0–5 years who are household contacts of MDR-TB cases. It is due to start in South Africa in October 2016.

8.3 New vaccines to prevent TB
Both the slow decline in TB incidence globally and the persistent threat of MDR-TB highlight the critical need for new TB vaccines that are more effective than the Bacille-Calmette-Guérin (BCG) vaccine in preventing TB. The status of the pipeline for new vaccines in August 2016 is shown in Fig. 8.3. The pipeline includes recombinant BCGs, whole-cell-derived vaccines, recombinant viral-vectorized platforms, protein and adjuvant combinations, and mycobacterial extracts. These vaccines aim either to prevent infection (pre-exposure) or to prevent primary progression to disease or reactivation of LTBI (post-exposure). Further details are provided below.

8.3.1 Phase II and Phase III clinical trials
There are currently eight vaccines in Phase II or Phase III trials.

**M72/AS01E**
M72/AS01E is made by GlaxoSmithKline (GSK) and is a recombinant fusion protein of the M. tuberculosis antigens...
The development pipeline for new TB vaccines, August 2015

MTBVAC
Biofabri, TBVI, Zaragoza

Ad5 Ag85A
McMaster, CanSino

ChAdOx1.85A / MVA85A
Oxford, Birmingham

MVA85A / MVA85A (ID, Aerosol)
Oxford

TB / FLU-04L
RIBSP

DAR-901
Dartmouth

H1/H56: IC31
SSI, Valneva, Aeras

H4: IC31
Sanofi Pasteur, SSI, Aeras

ID93 + GLA-SE
IDRI, Wellcome Trust, Aeras

VPM 1002
SII, Max Planck, VPM, TBVI

M72 + AS01E
GSK, Aeras

Vaccine™
Anhui Zhifei Longcom

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32 A and 39 A with the AS01E adjuvant. A large randomized placebo-controlled Phase IIb trial, conducted by GSK and Aeras, is enrolling pulmonary TB-negative, IGRA-positive, HIV-negative adults in Kenya, South Africa and Zambia. The primary end-point is the protective efficacy of two doses of M72/AS01E against pulmonary TB disease. Secondary end-points include safety and immunogenicity.

**H4:IC31 and H56:IC31**

The H4:IC31 and H56:IC31 vaccines are protein subunits with adjuvants, initially developed by the Statens Serum Institute (SSI) in Copenhagen, Denmark. H4:IC31 is being developed as a booster vaccine to BCG with Sanofi Pasteur. The vaccine candidate contains a fusion protein of Ag85B and TB10.4, formulated with the IC31 adjuvant. It is being tested in South Africa in a Phase II pre-proof of concept TB prevention study among IGRA-negative, HIV-negative adolescents at high risk of acquiring _M. tuberculosis_ infection; an intensive immunogenicity study is also being done in the same population. H4:IC31 is also being evaluated in a Phase I/II trial in infants.

H56:IC31 is an adjuvanted subunit vaccine that combines three _M. tuberculosis_ antigens (Ag85B, ESAT-6 and Rv2660c) with Valneva’s IC31 adjuvant, developed by SSI and Aeras. A Phase I study to evaluate its safety and immunogenicity in HIV-negative adults with and without LTBI and with no history or evidence of TB disease has been completed. Two Phase I trials have been completed to determine the safety and immunogenicity profile of H56:IC31 in HIV-negative, BCG-vaccinated adults with and without LTBI, and in patients who have recently been treated for pulmonary TB disease. These Phase I trials demonstrated an acceptable safety profile and found the vaccine to be immunogenic at all doses studied. A Phase II trial including H4:IC31, H56:IC31 and BCG in 84 adolescents is now under way.

**VPM 1002**

VPM 1002 is a live recombinant vaccine that was originally developed at the Max Planck Institute of Infection Biology, Germany, with further development by Vakzine Projekt Management, the Tuberculosis Vaccine Initiative and the Serum Institute of India. A Phase II trial is being implemented in South Africa to assess the safety and immunogenicity of the vaccine in HIV exposed and unexposed neonates. A Phase III trial for prevention of TB disease in adults is planned in India.

**RUTI®**

RUTI® is a non-live and polyantigenic vaccine based on fragmented and detoxified _M. tuberculosis_ bacteria. It is being developed by Archivel Farma as an immunotherapeutic vaccine, in conjunction with a short intensive antibiotic therapy. A Phase II trial in South Africa was completed recently, and other clinical trials are in the planning stages.

**DAR-901 booster**

The DAR-901 booster vaccine is a whole-cell, heat-inactivated, non-tuberculous mycobacterial vaccine, developed by Dartmouth and Aeras. It was shown to be effective in a Phase III trial in the United Republic of Tanzania among people who were HIV-positive. A Phase I booster trial in the United States of America among BCG-primed adults with and without HIV infection found that it was safe and well tolerated. With funding from GHIT-Japan, a 2-year Phase II trial among adolescents was initiated in April 2016 in the United Republic of Tanzania.
ID93 + GLA-SE
The ID93 + GLA-SE vaccine comprises three *M. tuberculosis* immune-dominant antigens (Rv2608, Rv3619 and Rv3620), one *M. tuberculosis* latency-associated antigen (Rv1813), and the adjuvant GLA-SE. It was developed by the Infectious Disease Research Institute in collaboration with Aeras. A Phase I trial in BCG-vaccinated, QuantiFERON-TB-Gold negative and positive healthy adults has been completed in South Africa. ID93 antigen (2 mg or 10 mg) in combination with GLA-SE adjuvant (2 mg or 5 mg), given as three doses, was found to have an acceptable safety profile in BCG-vaccinated health adults (both QuantiFERON negative and Quantiferon positive). Overall, significantly higher CD4+ responses were seen in all three intervention arms when compared with a placebo. A Phase IIa trial in South Africa, with the support of the Wellcome Trust, is evaluating safety and immunogenicity in HIV-naive TB patients that have recently completed treatment for pulmonary TB disease.

Vaccae™
The Vaccae™ vaccine is a specified lysate developed by the pharmaceutical company Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd. It has been licensed by the China Food and Drug Administration as an immunotherapeutic agent to help shorten TB treatment for patients with drug-susceptible TB. In collaboration with the Guangxi Center for Disease Control and Prevention in China, a Phase III trial is being implemented to assess its efficacy and safety in preventing TB disease in people with LTBI. It is the largest TB vaccine trial undertaken in the past decade, including 10,000 people aged 15–65 years with a TST >15 mm. The trial was scheduled to be completed by mid-2016.

8.3.2 Phase I trials
There are five vaccines in Phase I trials.

MTBVAC
MTBVAC is a live *M. tuberculosis* strain attenuated via deletions of the *phoP* and *fadD26* genes. It was developed by the University of Zaragoza, Institut Pasteur and Biofabri, with the support of the TB Vaccine Initiative (TBVI). The primary target population is neonates (BCG replacement vaccine), with a secondary target being adolescents and adults (booster vaccine). In September 2015, MTBVAC moved into a Phase Ib trial in infants.

Ad5 Ag85A
Ad5 Ag85A is an adenovirus serotype 5 vector expressing Ag85A, which has been developed by McMaster University with support from CanSino. It has been evaluated for safety and immunogenicity in 24 healthy human volunteers (both BCG-naive and previously BCG-immunized) in Canada. Overall, it was found to be safe, well tolerated and immunogenic in both trial groups, stimulating polyfunctional T-cell responses. More potent immunogenicity was observed in the previously BCG-vaccinated volunteers. A safety and immunogenicity study of the aerosol administration of this vaccine was recently completed.

TB/FLU-04L
TB/FLU-04L is a recombinant influenza vectored vaccine candidate that has been developed by the Research Institute for Biological Safety Problems and the Research Institute on Influenza in the Russian Federation. The influenza virus strain A/Puerto Rico/8/34 (H1N1) was used as a parent strain for construction of an attenuated replication-deficient vector expressing *M. tuberculosis* antigens Ag85A and ESAT-6. It was designed as a mucosal “boost” vaccine for infants, adolescents and adults. A Phase I trial in BCG-vaccinated QuantiFERON-TB-Gold negative healthy adult volunteers using intranasal administration was recently completed, and a Phase IIa trial is planned.

ChAdOx1.85
ChAdOx1.85 is a simian adenovirus expressing antigen 85 A, which was developed at the University of Oxford to boost BCG induced protection. It is being evaluated in a Phase I trial in BCG-vaccinated adults, both alone and as part of a prime-boost strategy with MVA85A.

MVA85A (Aerosol)
MVA85A (Aerosol) is an aerosolized vaccine MVA85A candidate that was developed at the University of Oxford. Its safety and immunogenicity has been tested in 24 BCG-vaccinated adults in the United Kingdom in a Phase I trial. The trial demonstrated that aerosol vaccination with MVA85A appears to be a safe and feasible compared with intradermal MVA85A, and produces a stronger CD4+ T-cell response than intradermal MVA85A. Further studies assessing the aerosol route are under way in people with LTBI.